SERUM TREATMENT OF EPIDEMIC CEREBRO-SPINAL MENINGITIS.*

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INTRODUCTION.

During the prevalence of the epidemics of cerebro-spinal meningitis in America and Europe from 1904 to 1907 *Diplococcus intracellularis,* discovered by Weichselbaum in 1887, was established finally as the cause of epidemic meningitis. In the course of the studies of this microorganism carried out by one of us (Flexner[1]), as one of a commission appointed by the Department of Health of the City of New York to investigate epidemic meningitis, an attempt was made to modify favorably the course of experimental infections with the diplococcus in animals by antisera prepared in several kinds of small animals from *Diplococcus intracellularies.* The ultimate purpose of these experiments was the employment of an antidiplococcus serum in the human infection once it was shown that it could be effective in the experimental infections. Flexner's first reports established that guinea pigs and monkeys, in which the conditions of the infection could be controlled, can be saved from otherwise fatal effects of the diplococcus by the use of the antiserum. Up to the time the first report was published a sufficient opportunity to test an antiserum in human beings had not appeared. Since then a diplococcus antiserum prepared by us in the horse has been tested upon several series of cases of epidemic meningitis, occurring in New York, Philadelphia, Cleveland, Castalia and Akron, Ohio, Edinburgh, Scotland, and Belfast, Ireland. The report which follows deals exclusively with the results of the use of the antiserum in human beings affected with epidemic meningitis.

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[1] *Jour. of the Amer. Med. Assoc.,* 1906, xlvii, 560. *The Jour. of Exper. Med.,* 1907, ix, 168.

The tests of the antiserum upon which this report rests could not have been carried out without the cordial coöperation of a considerable number of physicians who showed great interest in the undertaking. It will not be possible for us to thank personally, or even by name, all those participating in the tests and we will have, therefore, to content ourselves with the mention of those physicians who were very active in carrying them out. To Dr. L. W. Ladd, of Cleveland, who carried the antiserum to Castalia and Akron, Ohio, and who was the first to employ it systematically in a series of cases of meningitis, we feel an especial and deep obligation, on account of his early interest and the difficulties which he encountered in Castalia in following the cases which arose at widely separated points in a sparsely-settled country district. We are also grateful to Dr. Crile, of Cleveland, who brought to our attention the epidemic at Castalia and selected Dr. Ladd to administer the serum, to the physicians of the City Hospital of Akron, for their interest in the subject and the full reports which they supplied, to Dr. W. T. Longcope of the Pennsylvania Hospital, and Dr. B. F. Royer of the Municipal Hospital, Philadelphia, to Dr. L. Emmett Holt, of the Babies Hospital, and Dr. Strain of St. Vincent's Hospital, New York City, to Dr. Harvey W. Cushing, of Baltimore, Dr. Claude B. Ker, of Edinburgh, and Dr. A. Gardner Robb, of Belfast, and to the attending staffs at the several hospitals who permitted the trials to be made on their patients.

There will now follow the records of the cases of epidemic meningitis treated with the serum which are presented, with a few changes, in the precise form in which they came to us. The only alterations made in the reports consist of abbreviations of the hospital records where certain details could be omitted with a view of saving space and time, and the addition, at the end of each case, of a brief discussion, the purpose of which is to re-present the salient features with especial reference to the influence on the course of the disease exercised by the lumbar punctures and serum injections.

We regret that in some instances we have not yet received the full reports of cases treated with the antiserum, and are, therefore, restricted to the use of brief statements given in letters to one of us

(Flexner). These omissions are at present unavoidable and have been brought about by the great distances from New York at which antiserum is being tried, or by other circumstances which have temporarily caused withholding of the records. We believe that should the epidemic in America suffer a recrudescence the antiserum will receive a larger and more searching test; and, in any case, since the disease is still appearing sporadically over a wide territory in America and threatens to reappear in force in Great Britain, we expect to be able to publish a second and more complete report on the serum treatment of epidemic meningitis at no very distant date.

THE EPIDEMIC OF CEREBRO-SPINAL MENINGITIS AT AKRON, OHIO.

The epidemic at Akron began in April, 1907, and embraced about twenty cases of meningitis. We are greatly indebted to Dr. W. S. Chase for many of the facts on which are based our consideration of this epidemic. Between May 9 and June 16 there were reported to the health officer, as having been treated outside the hospital, nine cases of meningitis of which eight died and one recovered. Dr. Chase states that the patient who recovered presented atypical symptoms and no bacteriological examination of the spinal fluid was made. None of these cases received the antiserum.

Eleven cases of epidemic meningitis, established as such by symptoms and by bacteriological examination, were treated in the City Hospital with the antiserum. Eight of the cases recovered and three died. The period of first injection of the antiserum, the total amount of antiserum injected, and the mode of termination of the disease in the eleven patients are tabulated below.

Case	I,	1st injection	5th day;	total serum injection	82.5 c.c.;	recovery by lysis.
"	II.	"	30th hour;	" "	10.0 c.c.;	died.
"	III.	"	12th day;	" "	20.0 c.c.;	recovery by lysis.
"	IV.	"	2d day;	" "	43.5 c.c.;	recovery by lysis.
"	V.	"	7th day;	" "	25.0 c.c.;	recovery by crisis
"	VI.	"	2d day;	" "	22.5 c.c.;	died.
"	VIII.	"	1st day;	" "	35.0 c.c.;	recovery by crisis
"	VII.	"	1st day;	" "	15.0 c.c.;	died
"	IX.	"	2d day;	" "	105.0 c.c.;	recovery by lysis
"	X.	"	1st day;	" "	25.0 c.c.;	recovery by crisis
"	XI.	"	2d day;	" "	22.5 c.c.;	recovery by crisis

Two of the fatal cases were of the fulminating type, and one (Case VI) was injected first with the serum at the end of the second day and again on the fourth day of the illness and died three hours after the second injection. The fulminant cases died six hours and ten hours respectively after the first serum injection.

The total number of cases treated with the antiserum at Akron being eleven it is obvious that little value can be attached to the results stated in percentages. However, the following comparison may be made.

Nine cases of meningitis untreated with the antiserum: Eight or 89 per cent. died and one or 11 per cent. recovered.

Eleven cases treated with the antiserum: Eight or 72 per cent. recovered and three or 27.3 per cent. died.

Eliminating from the calculations the fulminating cases as being beyond reach of treatment, the figures obtained are:

Nine cases treated with the antiserum: Eight or 89 per cent. recovered and one or 11 per cent. died.

City Hospital, Akron, Ohio, Service of Dr. W. S. Chase.

CASE I. V. H. White female, aged 12 years. School girl.

Present Illness.—At 1 a. m. April 28, patient complained of pain in legs and stomach; at 4 a. m. became nauseated and vomited. She remained in bed during the greater part of the day and vomited frequently. Late in afternoon arose and walked out for 15 minutes. At 7 p. m. she became unconscious and voided urine involuntarily. She was restless and noisy until 2 a. m., April 30, when she slept for 2 hours; then the restlessness returned. Rigidity of neck and slight retraction of the head were first noticed on the 30th instant. Admitted to hospital that day.

Physical Examination.—Patient unconscious and restless and screaming, neck rigid, head retracted, pupils equal and react to light, patellar and abdominal reflexes absent, Kernig's sign marked, Babinski not present, herpes on lips. Temperature 99.6°, pulse 100, respiration 24.

May 1. Totally unconscious, restless and noisy; temperature ranged from 99.6° to 102.2°; pulse from 92 to 160.

May 2, 10 a. m. Lumbar puncture, 15 c.c. of opalescent fluid withdrawn. Microscopical examination showed Gram-negative diplococci within and outside of pus cells. Temperature from 99.6° to 102°.

May 3. Condition unchanged.

May 4, 6 a. m. Temperature 101.8°.—8.30 a. m. 10 c.c. opalescent fluid withdrawn by lumbar puncture and *10 c.c. antimeningitis serum injected.*—10 a. m. Temperature 100°.—10.40 a. m. Convulsion involving face, eyes and left hand lasting two minutes.—11.21 a. m. Second convulsion, which continued until relieved with chloroform.—1.50 p. m. Continuous nystagmus of both eyes; twitch-

ing of arms and upper lip; reflexes of extremities and cornea absent.—3 p. m. Convulsions continue except when controlled with chloroform. Kernig's sign more marked than before; rigidity of neck increased; convulsions controlled with chloroform until 5.30 p. m., nystagmus continuous between convulsions.—6 p. m. Temperature 102.2°.—8 p. m. 99.8°.—8.45 p. m. Conscious.—9.30 p. m. Convulsion controlled with chloroform.—12 midnight. Temperature 98.2°.

May 5. Temperature did not rise to 100° until 9 p. m. Patient slept from 12.30 a. m. to 3 a. m. Still some twitching of mouth and left eye. At 4 a. m. took water on being aroused. At 6 a. m. complains of thirst and asks constantly for water and milk.—7 p. m. The patient has taken freely of milk and water during the day and cries for food. She has rested well until midnight. Temperature below 100° until 9 p. m., when it was 100°, and at midnight 101.4°.

May 6. Rested fairly well; condition improved; took considerable nourishment.

May 7 and 8. No essential change.

May 9. Restless after midnight, complains bitterly of frontal headache; temperature rose at 12 m. to 102.8°, and at 3 p. m. to 103.4°.—9 p. m. Temperature 103.8°; lumbar puncture under chloroform anæsthesia, 30 c.c. opalescent fluid withdrawn and *7.5 c.c. antiserum injected.*—10.30 p. m. Temperature 101.8°.—12 midnight. 101.6°.

May 10, 2 a. m. Slight twitching of hands; vomited. Rested well and took nourishment during the day; temperature normal to subnormal.

May 11. Temperature remained below 100°; patient rested well.

May 12, 3 a. m. Temperature 100°; very restless and noisy. Temperature rose during the day.—9 a. m. 102.8°.—12 m. 103.6°.—9 p. m. 104.2°. Withdrew, under chloroform anæsthesia, 60 c.c. opalescent spinal fluid, in which diplococci were not found on microscopical examination, and injected *7.5 c.c. of the antiserum.*—12 midnight. Temperature 102°.

May 13. Patient had a good day and the temperature was 100° at 6 a. m., normal at noon and 97° at midnight.

May 15. Complains of bad headache; temperature rose in afternoon to 104° (3 p. m.).—9 p. m. Temperature 103.2°, lumbar puncture yielding 22 c.c. opalescent fluid free of diplococci.—12 m. Temperature 103.8°.

May 16. Temperature remained above 100° until 9 p. m. Vomited several times; very restless. The condition fluctuated, but remained essentially unchanged until May 25. The rigidity of the neck continued and Kernig's sign was still present and the reflexes had returned in some degree. Pain was still complained of in the head and other parts. The temperature fluctuated between 99° and 102.5°. At 11 a. m. 90 c.c. of less opalescent fluid were withdrawn by lumbar puncture and *20 c.c. of antiserum injected.* The spinal fluid contained leucocytes but no diplococci. At 8 p. m. marked urticaria developed. The patient vomited and was restless and noisy during the afternoon. The temperature fell and reached normal at 12 p. m. the next day. The temperature remained at normal or a little below for four days, then rose to 101.8°, and fell in a few hours. The general condition was better.

June 1. Herpes appearing on lips; neck rigidity lessened; Kernig's sign still marked. Temperature fluctuated between 99.4° and 101°.

June 3. Restless, noisy, complains of pain. Temperature rose suddenly at

9 p. m. to 103°.—11 p. m. Lumbar puncture under chloroform anæsthesia. 75 c.c. of fluid withdrawn and *15 c.c. of antiserum injected.* The spinal fluid showed on microscopical examination a few diplococci and a very small number of leucocytes. Temperature at midnight 100.4°. The temperature was normal June 4, and did not rise above again. The note on June 9 reads: "Patient's condition greatly improved; she is rational and quiet all the time, the reflexes are normal, Kernig's sign is absent, the rigidity of the neck has disappeared, there is complete absence of all pain, and all the functions appear to be normal. The patient states that she feels well."

June 10 to 14. The note states that the temperature has remained practically at normal; sleep is good, but there is some complaint during the day of pain in various parts; the reflexes are normal and Kernig's sign is absent, but there is involuntary movements of bowels and bladder.

June 15. The note states that the patient still complains of pain and is very restless and noisy. The temperature is about normal. 2 p. m. Headache and vomiting. At 3 p. m. lumbar puncture was performed and 75 c.c. of spinal fluid were withdrawn. Microscopical examination showed "many extracellular diplococci and no leucocytes." *22.5 c.c. of antiserum injected.* The next notes are given entire.

"From June 17 to 25, inclusive, the temperature ranged from normal to 101.6°. The latter temperature was reached on the 18th instant; after that it did not again reach 100°. Appetite was good. Pain in the ear and abdomen complained of responded to palliative treatment. Involuntary micturition and bowel movements continued. On the 25th the patient sat up in bed without discomfort."

"Beginning June 26 (58th day of disease) the temperature remained normal until the day of discharge (96th day of disease). After June 28 the involuntary movements ceased. . . . On 96th day the patient was examined and found well; discharged. She reports to hospital twice weekly, and she is in excellent condition."

Discussion.—This case is one of severe and protracted epidemic meningitis. The diagnosis is clearly established by the symptoms and the bacteriological examination. The special interest which the case has for us is involved in the question whether its course was essentially influenced by the several injections of antimeningitis serum. It does not seem possible to give a definite and outright answer to this question. On the other hand the following points appear to be clear: The first injection of serum (on May 4) was followed by severe convulsions enduring during a large part of the day and requiring to be relieved by chloroform. The convulsions did not re-appear spontaneously and were not excited by subsequent injections of larger amounts of the serum. It is probable, therefore, that the association was accidental. The serum injections generally were followed by a fall in the temperature which reached

or approached the normal and remained at these levels for several days. The temperature and symptoms were subject to much fluctuation, but when the former rose approximately to 104° and the latter became severe, lumbar puncture and serum injection were followed by a tolerably prompt improvement in the patient's condition. On one occasion (May 15), lumbar puncture was performed and no serum injection made and it is noteworthy that the temperature did not fall as in the instance in which the serum injection followed the puncture. The condition of the patient becoming unsatisfactory on May 25 a puncture and serum injection being carried out the temperature fell promptly, remained at or about normal for several days, and the patient's general condition was described as improved. These different results may mean nothing actually, but we put them together since it is desirable to secure light on the independent effects of the puncture alone and the puncture plus the serum injections. Note should be taken of the occurrence of urticaria following the serum injection of May 25. The clearing up of the cerebro-spinal fluid, following the puncture and serum injections, and the disappearance from it of many leucocytes and all *demonstrable* diplococci before the subsidence of the symptoms is shown to be possible. The final history of the case indicates that there may still remain an active focus in the membranes from which a fresh invasion of diplococcus into the spinal fluid may take place, with which is associated a reappearance of certain symptoms and a sudden rise in temperature. Such a relapse would seem to have occurred on June 3 and not to have been attended by a rich outpouring of leucocytes into the cerebro-spinal fluid. If this observation is admitted it is at least worth noting that the condition was quickly controlled by the puncture and serum injection although it is not established that these means were the sole or chief causes of the abrupt termination of the relapse. Only an accurate and painstaking clinical and bacteriological study of protracted and relapsing cases of epidemic meningitis will suffice to determine the manner in which, and the rapidity with which the body's forces unaided deal with the diplococcus. Total amount of antiserum injected, 82.5 cubic centimeters.

City Hospital, Akron, Ohio. Service of Dr. George Rankin.

CASE II. H. R. White male, aged 17 years. Rubber worker.

Present Illness.—Admitted May 9, 1907, 12 m. The day before admission the patient was at his work, but in the evening he complained of headache and feeling ill, and he went early to bed. At 4 a. m. his family was aroused by his falling out of bed. He was picked up in an unconscious state. He was seen at 9 a. m. by a physician who found him unconscious, restless, throwing himself about, and with a temperature of 104° F. Still unconscious and tossing about on admission to hospital at 12 o'clock noon.

Physical Examination.—Face flushed; perspiring freely; pupils moderately dilated, do not react to light; neck rigid and slight retraction of head; abdominal, patellar and plantar reflexes absent; Kernig's sign present.

May 9, 1 p. m. Temperature 101.6°, pulse 90, respiration 40. Lumbar puncture yielded 60 c.c. of opalescent fluid containing pus cells and extra- and intracellular diplococci.—3 p. m. Temperature 101.6°. Vomited several times during the afternoon; pulse could not be counted during afternoon.—6.30 p. m. Temperature 102.8°.—9 p. m. 103°.—12 midnight. 105.4°, respiration 70. At 11 p. m. lumbar punctured and 60 c.c. opalescent fluid withdrawn and *10 c.c. of antiserum injected.* The microscopical examination of the fluid gave the same results as the first fluid withdrawn. The pulse continued uncountable and the respiration high. Temperature at 3 a. m. 106.2°, at 5 a. m. 107.2°; died at 5.42 a. m. May 10.

Discussion.—This case is an example of the fulminating type of epidemic meningitis. From the appearance of the marked symptoms and the death, less than 36 hours elapsed. At the time of the second lumbar puncture and the first injection of the serum the patient was in a critical condition and survived these operations only six hours. It is highly improbable that the serum could influence favorably so severe an infection as existed in this case, but it would have been proper to have injected it earlier—immediately after the first lumbar puncture had established the diagnosis—and in much larger quantity. The reason that the serum was not injected earlier is found in the fact that it had first to be brought from Cleveland; and that the dose was small is explained by the date of the serum's employment, for at that time it was being used very cautiously since we had not yet learned that it could be injected in much larger amount with impunity into the inflamed spinal canal of human beings. Total amount of antiserum injected, 10 cubic centimeters.

City Hospital, Akron, Ohio. Service of Dr. W. S. Chase.

CASE III. B. S. White male, aged 19 years. Rubber worker.

Present Illness.—Until May 11, 1907, the patient was well. On that day he felt badly, went to bed early and was said to have had a chill during the night. No further history of illness until May 13, when a physician saw the patient who was feverish, restless and complained of pain in head and neck. That night he became unconscious; admitted to hospital next morning (May 14). He was, at that time, unconscious and irrational and very restless, tossing and talking continuously. "Temperature 99°, pulseless at wrist, respiration 32 and shallow, cyanosed."

Physical Examination.—Unconscious and greatly cyanosed young man. Heart beats 56 per minute. Neck somewhat rigid and painful on being moved. Reflexes diminished.

May 14. Temperature varied from 99° to 101.6°. Under stimulants, pulse improved; at 12 p. m. 104, at 12 a. m. 88.

May 15 and 16. Condition essentially unchanged.

May 16. Reflexes absent from extremities and abdomen; neck rigidity marked; Kernig's sign present. Lumbar puncture unsuccessful. Restless and talking.

May 23. Note states: "Patient semi-conscious part and conscious other part of the time. The reflexes, except the plantar reflex, are absent. Neck rigid and painful on being moved. Temperature fluctuated from 99° to 102.4°. Slept and rested well and took considerable nourishment."

May 24. Temperature rose to 103.4°; otherwise no change.

May 26. No marked change. Kernig's sign present; reflexes absent. Temperature at 12 p. m. 103.6°. Lumbar puncture performed under local anæsthesia and 60 c.c. opalescent fluid obtained and *20 c.c. antiserum injected.* The examination of the spinal fluid showed pus cells and extra- and intracellular diplococci.—3 p. m. Temperature 103.2°.—6 p. m. 102.8°.—9 p. m. 102°.—12 a. m. 99.8°. Patient rested well, perspired freely and took considerable nourishment during the night.

May 27. Temperature ranged from 98° to 99.2°. The note states: "Mental condition improved; reflexes not changed; slept well and took considerable nourishment."

May 28. Temperature ranged from 97° to 97.8°. The note states: "Reflexes are now normal; the mental condition is good, but the neck is still somewhat rigid and slightly painful on being moved."

The next note states that from May 29 to June 6, the date of discharge from the hospital, the patient's condition continued to improve and there was complete recovery.

Discussion.—This case is an example of epidemic meningitis with severe onset and gradual subsidence of symptoms by lysis. The indications are that the patient's recovery was reasonably assured before the successful lumbar puncture and injection of the serum on the twelfth to the fourteenth day of the disease. Until the day of injection the temperature had not remained continuously, during any

one day, below 101°. Within twelve hours of the injection the temperature fell below 100° and did not again rise to that point, tending rather to remain somewhat subnormal. Whether this is more than a coincidence cannot be decided now. The quick return of the reflexes following the puncture and serum injection, and the acceleration of the rate of improvement in the patient's mental and general condition, may also be merely co-incidental, but they were sufficiently great to be regarded as noteworthy. Total amount of antiserum injected, 20 cubic centimeters.

City Hospital, Akron, Ohio. Service of Dr. L. R. C. Eberhard.

CASE IV. B. K. Female, aged 15 years. Factory worker.

Present Illness.—Patient felt well and worked until May 14, 1907. Awoke 6 a. m. May 15 feeling ill and complaining of headache; ate little breakfast; returned to bed, vomited and became unconscious during the day. Physician called; found temperature 101.4°; patient restless and irritable and crying out with pain on being touched. Admitted to hospital May 16. She was unconscious and tossing about. The abdominal reflex was absent and the patellar and plantar reflexes greatly diminished. The neck was somewhat rigid and attempts to move it were very painful.

May 16, 9 a. m. Temperature 103.8°, pulse 84, respiration 34.—10.30 a. m. Lumbar puncture under chloroform anæsthesia; 45 c.c opalescent fluid containing pus cells and extra- and intracellular diplococci withdrawn. *15 c.c. of antimeningitis serum injected.*—12 p. m. Temperature 102°. It ranged during the rest of the day from 101° to 102.6°.

May 17, 3 a. m. Temperature 99.6°; 10 a. m. 100.8°; 5 p. m. 102.2°; 12 a. m. 102.6°. The note states: "Patient slept part of the night, but is restless at times. Knee, plantar and abdominal reflexes are present. There is marked Kernig's sign and no Babinski reflex; no ankle clonus. Restless and noisy from 9 p. m. to midnight."

May 19, 8 a. m. Unconscious and irrational except when spoken to. Herpes on lips. Internal squint of right and left eyes.—7.30 p. m. Lumbar puncture under chloroform anæsthesia; 45 c.c. of opalescent fluid withdrawn and *5 c.c. antiserum injected.* Slept from 11 p. m. to 5 a. m.

May 21. Condition has remained essentially unchanged. Temperature, 9 a. m., 103.2°.—9.30 a. m. Lumbar puncture: 3.5 c.c. fluid withdrawn and *3.5 c.c. serum injected.* Spinal fluid shows diplococci.—7 p. m. Condition unchanged.

May 22. Patient irrational and complains more than previously on being moved. She seems not to have control of the arms, although she moves hands, fingers and legs.

May 25. Condition has not changed materially. 9.30 a. m. Lumbar puncture under chloroform; 75 c.c. of opalescent fluid removed; *20 c.c. of antiserum injected.* Temperature during the day ranged from 99.6° to 102.8°.

May 26. Temperature ranged from 99.8° to 102°.

May 27. 99° to 102.6°. The note at 6 p. m. states that all reflexes are present, that the left arm cannot be used and the left trapezius is contracted, drawing the

head to the left side. Patient is conscious and rational and rested well. Kernig's sign is present.

May 27. Urticaria has appeared on knees and elbows. The temperature has remained below 100° since 3 a. m.

May 29. Temperature below 100°.

June 1. The temperature has remained below 100° except for one or two brief intervals, when it reached that height. Patient is conscious and rational. All reflexes except the abdominal reflex are present, the neck is less rigid and can be moved voluntarily as can the arms and legs. Kernig's sign still present.

June 5. Temperature has remained below 100° (all temperatures until to-day taken per rectum). Axillary temperature normal.

June 9. Patient improved in every way. Reflexes normal. Kernig's sign absent. Rigidity of neck gone. Has use of all extremities and functions appear to be normal. Urticaria appeared over entire body.

June 10. The final note states that temperature and pulse remained normal and the patient was discharged well on June 27, the forty-first day after admission.

Discussion.—This case is an example of epidemic meningitis with severe onset, moderately prolonged illness, subsidence of symptoms by lysis and complete recovery. The patient was admitted to the hospital about 24 hours after the appearance of the first severe symptoms, and the diagnosis was established by lumbar puncture and a first dose of antiserum administered within the first thirty hours of the disease. No marked or permanent influence on the course of the disease, as far as can be determined, was produced by the puncture and serum, and subsequently three additional injections of serum (following withdrawal of fluid) were made into the spinal canal. On May 25, or approximately the tenth day of illness, an injection of 20 c.c. of serum was given (the two previous injections were of 3.5 c.c. and 5 c.c. respectively). On May 26, the note states that the reflexes, which had previously been absent, had returned, but the same note records the involvement of the trapezius muscle in the rigidity of the neck. May 27 the temperature remained persistently below 100°, and from that date on no rise of temperature above 100° (rectal measurements) was recorded. Urticaria appeared on that day. The condition of the patient improved more or less in the next days and on June 1, the symptoms had considerably abated, voluntary muscular movements had returned and the neck was less stiff. The disappearance of Kernig's sign and the general functional restoration of the body

are noted on June 9 when the patient was regarded as convalescent. It is not possible to assign the specific influence, if any was exerted, of the serum on the progress and final result in this case. Total amount of antiserum injected, 43.5 cubic centimeters.

City Hospital, Akron, Ohio. Service of Dr. W. S. Chase.

CASE V. F. N. White male, aged 32 years. Laborer.

Present Illness.—The patient had been well, except for coryza, until May 12, when he felt ill and suffered from pain in the muscles and head. May 13 consulted physician who said he had fever and who gave him a purgative and sent him to bed. Did not go to work, felt chilly, vomited, complained of pain in head and neck. Next day no better, but he went to his work and remained until noon. He was obliged to return to bed, where he remained until May 16, when his mental condition becoming alarming he was taken to hospital. Patient became unconscious in the ambulance.

Physical Examination.—Unconscious; neck rigid; reflexes absent; Kernig's sign absent; head slightly retracted; pupils somewhat contracted, react sluggishly to light. Temperature, 4 p. m., 104.2°; 12 a. m. 102.2°. Delirious.

May 17. The note states that the patient was restless, noisy and delirious, and Kernig's sign was now present.—3 p. m. Lumbar puncture attempted, but no fluid was obtained. At 2 p. m., out of bed, delirious, put in restraint.

May 18. Neck very rigid, otherwise condition unchanged.

May 21. The condition fluctuated during the past four days; the temperature ranged from 98.6° to 104.4°, pulse up to 130, respiration rapid and irregular, and there were delirium, noisiness and restlessness. The physical signs have not changed; hiccough has appeared.

May 22, 10 a. m. Under chloroform anæsthesia lumbar puncture was made and 90 c.c. of cloudy fluid, which was under considerable pressure, were removed. At the same time *25 c.c. of antiserum were injected.* The spinal fluid showed on microscopical examination pus cells and intra- and extracellular diplococci.—12 m. Temperature 100.8°; pulse 104.—12 a. m. Temperature 102°; pulse 98.

May 23. The note states that the patient rested fairly well after midnight. At 9 a. m. he was conscious and resting quietly and the mental condition was improved. He was free from pain and the reflexes were unchanged. Temperature: 3 a. m. 101.4°, 12 p. m. 100°, 12 p. m. 98°.

May 24. Rested well part of night and day. Conscious and rational. Knee and plantar reflexes present. Kernig's sign still present. Neck still somewhat rigid and painful on being moved. Temperature normal since midnight.

May 25. Temperature normal. The patient has slept well and taken freely of nourishment.

The next note states that from May 25 to June 5 the temperature and pulse were normal; the patient was up and about the ward since June 2, the reflexes were normal, there was no rigidity and no Kernig's sign.

June 6. Patient awoke at 3.30 a. m. complaining of pain in legs and back. He was unable to move his legs and complained of pain when they were moved. Reflexes could not be elicited, but legs were held rigidly. Pain and tactile sensations normal.

June 7. Extremities less painful, but there is marked tenderness over the large nerve trunks.

June 8. Functions of lower limbs gradually returning.

June 12. The patient is improving, the neuritis is diminishing and the extremities can be used.

June 15. Patient discharged cured.

August 2. Patient has reported to the hospital. He is in perfect health.

Discussion.—The onset of the symptoms of meningitis was in this case gradual and extended over 3 days. The symptoms became severe on May 16 and the patient's condition was bad until May 23 when it suddenly and critically changed for the better. From May 23 on the patient's condition continued to improve, with the exception of the discomfort caused by the neuritis which appeared in the legs on June 6 and quickly subsided, until June 15 when he was discharged "cured" from the hospital. The meningeal and mental symptoms and the symptoms of general intoxication were, in this case, profound. On May 22, or approximately the seventh day of the disease, successful lumbar puncture was made and the antiserum injected. Twenty-four hours later the patient's condition was described as improved and the level of the temperature was lower than before. The condition of the reflexes was, however, unchanged. Within forty-eight hours of the puncture and serum injection the patient had become conscious and rational, the reflexes had in part returned, the neck was less rigid, the temperature reached normal, and the patient was resting quietly, sleeping and taking nourishment. No rise in the temperature again occurred. The patient was evidently convalescent. The critical disappearance of the severe symptoms and the lumbar puncture and injection of serum would seem to bear some relation to each other. There was an abrupt transition from a condition of much seriousness, which had endured unchanged for a week, to one of comparative and actual mildness within forty-eight hours of the puncture and injection of the antiserum. Total amount of antiserum injected, 25 cubic centimeters.

City Hospital, Akron, Ohio. Service of Dr. W. S. Chase.

CASE VI. Z. H. White female, aged 17 years. Rubber worker.

Present Illness.—The patient was at work until May 18, when she went home on account of malaise and pain in back and limbs. At 2 a. m. the next morning

she complained of severe headache, at 3 a. m. she became unconscious. A physician was called at 7 a. m. (May 19). He said she had fever. During the day she vomited frequently. Axillary temperature, 3 p. m., 104°. Admitted to hospital 6 p. m.

Physical Examination.—Patient admitted in an unconscious state. She is very restless, tosses and rolls her eyes continuously. Knee and plantar reflexes present; abdominal reflex absent; Kernig's sign present.

May 20. Temperature, 9 p. m., 101.2°. Under chloroform anæsthesia 45 c.c. of spinal fluid were withdrawn by lumbar puncture and *15 c.c. antiserum injected.* The fluid showed pus cells and extra- and intracellular diplococci.—12 p. m. Temperature 99.2°.

May 21. Patient conscious and rational; complains of frontal headache. Pupils equal and react; abdominal reflex absent; patellar diminished, plantar present. Kernig's sign marked. Babinski sign absent; ankle clonus absent. Neck rigid and painful on movement. Temperature has risen above 99°.

May 22. Patient's mental condition less good than yesterday. Herpes appearing on lips. Large hyperæmic areas have appeared on abdomen. Temperature during the day has fallen to 99.8°.—10.30 p. m. Under chloroform anæsthesia withdrew 7.5 c.c. of spinal fluid and injected *7.5 c.c. of the antiserum.*—12 a. m. Temperature 99.2°.—12.30 a. m. Patient had been resting fairly well when the nurse's attention was attracted by gasps and before a physician could reach her side she died. No autopsy was permitted.

Discussion.—The symptoms of meningitis came on quickly and were severe in type and lumbar puncture and a serum injection were made about 45 hours after their first appearance. Following the puncture and serum injection the temperature remained constantly below 100° and the patient regained consciousness. A second puncture and serum injection were made about 48 hours after the first. About two and a half hours after these the patient suddenly died. No autopsy was obtained and the immediate cause of death was not established. Total amount of antiserum injected, 22.5 cubic centimeters.

City Hospital, Akron, Ohio. Service of Dr. A. F. Sippy.

CASE VII. H. S. White male, aged 14. Schoolboy.

Present History.—Patient complained of headache on May 21. The next day he vomited and suffered pain in back of head. Temperature, 11 a. m. 101°; delirious at 5 p. m. Admitted to hospital at 8 p. m.

Physical Examination.—Temperature 104°, pulse 120, respiration 44. Wildly delirious; pupils dilated, do not respond to light. Reflexes absent; Kernig's sign positive; some rigidity of neck.

May 22, 9 p. m. Under chloroform anæsthesia 75 c.c. of opalescent spinal fluid withdrawn and *15 c.c. of antiserum injected.* The spinal fluid contained pus cells and extra- and intracellular diplococci. Temperature, 12 a. m., 103°; pulse 100; respiration 30.

May 23. Patient slept until 2 a. m., after which time he was restless. Temperature: 3 a. m. 102.4°, 9 a. m. 99° 9 p. m. 100° (by rectum).

May 24. Temperature: 12 p. m. 100.6°, 9 p. m. 99.8°. Pulse 60 to 78. Vomited twice; rested fairly well.

May 25. Patient slept fairly well after-part of night; complains of headache. Neck rigid and painful on motion; pupils react to light. Patient conscious and rational. Temperature: 1 a. m. 103°, 9 a. m. 102°. At 10 a. m. 75 c.c. of opalescent spinal fluid withdrawn and *20 c.c. antiserum injected.* Microscopical examination of the spinal fluid showed leucocytes and diplococci. Temperature: 12 p. m. 100°, 6 p. m. 99°, and 12 p. m. 98.6° (mouth).

May 26. Temperature normal. Patient slept well after-part of night; conscious and rational; rests quietly; all reflexes present; neck less rigid than earlier in attack.

May 27 to June 1. The temperature has remained normal and his condition satisfactory. Note on June 2 states that the patient is apparently well, the reflexes are normal and the rigidity of the neck has gone.

The final note states that from June 3 to June 8, the day of discharge from hospital, the temperature remained normal and recovery was perfect.

Discussion.—The patient was brought to the hospital during the first day of illness and the diagnosis of meningitis was established by lumbar puncture and the first dose of serum administered in little more than 24 hours after the illness began. The subsequent course of the infection was mild. On the fourth day of illness (May 25) the temperature having risen to 103° F. a second puncture and serum injection were made. Less than twenty-four hours later the temperature had fallen to normal and the general condition of the patient had improved. There was no subsequent rise in the temperature, all the symptoms rapidly subsided, and recovery was complete. Total amount of antiserum injected, 35 cubic centimeters.

City Hospital, Akron, Ohio. Service of Dr. W. S. Chase.

CASE VIII. R. M. White male, aged 17 years. Electrician with rubber company.

Present Illness.—On May 24 left his work at noon on account of feeling ill. Went home, refused supper, vomited during the evening, and went to bed early on account of headache. Restless during the night. Headache more severe next morning; vomited again, and became unconscious about 10 a. m. Admitted to hospital 1 p. m.

Physical Examination.—Well-developed, muscular man. Pupils slightly contracted; equal; react to light. Neck somewhat rigid and painful on being moved. Knee reflex exaggerated, plantar reflex present, abdominal reflex absent. Kernig's sign present. The patient is very violent and tosses on the bed.

May 25, 2 p. m. Temperature 105.2°, pulse 142, respiration 20. Under chloroform anæsthesia 15 c.c. of spinal fluid withdrawn and *15 c.c. of antiserum injected.* The spinal fluid showed leucocytes and extra- and intracellular diplococci.—6 p. m. Temperature 104.8°, pulse 134.—9 p. m. Temperature 102.4°, pulse 130, respiration 20, cyanosed. Aromatic spirits of ammonia and ether administered hypodermically. Respiration ceased; artificial respiration and oxygen inhalation; respiration continued from 6 to 8 per minute; death at 12.30 a. m.

Discussion.—The preceding case is an example of the fulminating type of epidemic meningitis in which from the first appearance of severe symptoms and death about 24 hours elapsed. Lumbar puncture and serum injection were made about 10 hours before death and were without appreciable effect on the course and termination of the infection. Total amount of antiserum injected, 15 cubic centimeters.

City Hospital, Akron, Ohio. Service of Dr. George Rankin.

CASE IX. J. A. S. White male, aged 24 years. Mail carrier.

Present Illness.—Until two days before admission to hospital patient has been in good health. He ascribed headache and malaise to exposure to hot sun. June 23 had intense headache, nausea, vomiting and pain in back of neck. About 11.30 p. m. became unconscious. Temperature 103°. Admitted to hospital June 24, 11 a. m.

Physical Examination.—Patient violently delirious; requires to be restrained. Had involuntary bowel and bladder movements. Abdominal and patellar reflexes absent; plantar reflex diminished. Neck rigid; painful on being moved. Kernig's sign present. Pupils equal, moderately dilated, react to light.

June 24, 11 a. m. Temperature 103.8°, pulse 70, respiration 36.—1 p. m. Under local anæsthesia 90 c.c. of spinal fluid removed and *22.5 c.c. antiserum injected.* Pus cells and diplococci chiefly within the cells found on examination of the spinal fluid. Temperature: 3 p. m. 100.8°, 12 p. m. 101.4°.

June 25. Patient slept fairly well under an anodyne during the latter part of the night. Note at 8 a. m.: "Patient quiet and semiconscious, responds when spoken to but mutters unintelligibly when attempting to form sentences. Knee jerk not elicited; plantar reflex diminished; abdominal reflex present for first time since admission. Neck rigidly increased." The temperature fluctuated from 99.6° (6 p. m.) to 101.2°.

June 26. Patient restless during night; conscious and rational part of time; neck held less rigidly. The temperature has risen: at 12 p. m. 102.2°, at 12 a. m. 103° (per rectum).

June 27. Restless; extremities cold. 3 a. m. lumbar puncture under chloroform anæsthesia; 45 c.c. of spinal fluid withdrawn and *22.5 c.c. antiserum injected.* A chill followed lasting 20 minutes. Herpes appearing on lips. The temperature has fluctuated between 102° and 103° all the day.—9 a. m. "The patient in exceptionally cheerful mood, singing and talking, but entirely rational when spoken to."

June 28. Condition essentially unchanged.

June 29. Temperature at a slightly lower level.

June 30. The note reads: "Condition good; perfectly conscious and rational; reflexes all present; Kernig's sign still marked; neck quite rigid and painful on movement; headache; extensive herpes labialis." The temperature fluctuated between 101° and 103.2°.

July 1. Condition about the same.

July 2, 6 p. m. Temperature: 103.4°, 9 p. m. 103.2°. Under chloroform anæsthesia 60 c.c. spinal fluid, containing diplococci, withdrawn and *30 c.c. of antiserum injected.*—12 a. m. Temperature 101.8°.

July 3. The temperature reached 99° and has run at a lower level than previously.

July 4. The temperature (rectal) has remained below 100° all day. Otherwise the condition is not markedly changed.

July 5. The temperature has fluctuated to-day, having reached 102.2° at 9 a. m., but remaining below 100° for the most part.

July 6. The temperature has risen again. At 6 a. m. it was 103.8°; patient did not rest well; the neck rigidity has lessened; mental condition good. Kernig's sign still present.—12 p. m. Temperature 103.4°. At 2 p. m. 45 c.c. of spinal fluid were withdrawn and *30 c.c. of antiserum injected.* Stained specimens of the spinal fluid show very few leucocytes containing diplococci and extracellular diplococci.

July 7. Temperature at a lower level, but general condition not essentially changed.

July 8. Patient rested well. The temperature has been below 100° most of the day.

July 9 and 10. Temperature has not risen and condition of patient improved.

July 11 and 12. The temperature has remained normal.

The final note reads: "July 13 to July 27, the date of his discharge from the hospital, the patient continued to improve. When discharged he complained only of not feeling strong. On August 24, when he reported to the hospital, he was well but had not recovered usual strength. On September 8 he had not yet reported for work."

Discussion.—This case of epidemic meningitis ran a moderately severe and protracted course and the symptoms gradually subsided. The particular influence of the spinal punctures and serum injections cannot be defined. The disease terminated favorably and recovery was complete. The conditions under which the serum was employed were favorable to its action since the first injection was made within 48 hours of the onset of severe symptoms. Four injections of the serum were made without the appearance of unpleasant effects. On the other hand the temperature tended to seek a lower level after the injections. The third injection, on the tenth day of illness, was followed by a fall in the temperature

which persisted for four days. When it again rose to 103.4°, on the fourteenth day a fourth injection of the serum was made after which the temperature fell below 100° and soon reached normal where it remained. Convalescence may be said to have begun on the sixteenth day of the illness. Total amount of antiserum injected, 105 cubic centimeters.

City Hospital, Akron, Ohio. Service of Drs. Kobler and Seiler.

CASE X. E. R. White male, aged 20 years.

Present Illness.—The illness began with headache and nausea about noon. After midday meal the patient went to bed and at 3 p. m. was found unconscious and in a violent state. Admitted to hospital the same day (June 30, 1907) at 9.50 p. m.

Physical Examination.—Unconscious and violently excited man moaning constantly. Knee and plantar reflexes exaggerated; Kernig's sign positive; neck slightly rigid; pupils moderately dilated; react to light.

June 30, 10 p. m. Did lumbar puncture under chloroform anæsthesia and withdrew 75 c.c. of spinal fluid and injected *25 c.c. antiserum.* Microscopical examination of the fluid showed polynuclear leucocytes and many intra- and extracellular diplococci. Temperature: 10 p. m. 100.2°, 12 a. m. 99°.

July 1, 2 a. m. Convulsion lasting 20 minutes. During the day patient vomited several times. The temperature did not rise above 100°.

July 2. The temperature has been below 100° all day and much of the time has been normal. The note reads: "Condition of patient markedly improved; he is conscious and rational, all the reflexes are present, Kernig's sign is less marked than it was, the neck is still stiff and painful, headache still persists, and the mental condition is good. Considerable nourishment was taken during the day."

July 3. The temperature has remained below 100° and much of the time was normal. The general condition is as on yesterday.

July 4. Patient rested well; he complains less of pain. Temperature normal.

July 5. The note reads: "Patient slept well; general condition good; reflexes normal; Kernig's sign and neck rigidity absent; mentality normal."

The patient continued to have normal temperature and was discharged on July 11 "cured," twelve days after having entered hospital.

Discussion.—The onset of the symptoms in this case was abrupt and severe. From the appearance of the premonitory headache and malaise to the lumbar puncture and serum injection hardly more than twelve hours had elapsed. Following upon the puncture and the injection of serum the symptoms abated rapidly and the patient may be said to have been over the disease within forty-eight hours of its onset. No reasonable doubt can exist regarding the diagnosis in view of the symptoms present and the results of

the bacteriological examination. Total amount of antiserum injected, 25 cubic centimeters.

City Hospital, Akron, Ohio. Service of Drs. Theiss and Sippy.

CASE XI. G. G. White female, aged 17 years. Schoolgirl.

Present illness.—Twenty-four hours before admission to the hospital she began to complain of malaise and headache. During the night she vomited and the symptoms grew gradually worse until 2.30 p. m. when she became unconscious. Admitted to hospital at 7 p. m. June 9.

Physical Examination.—The patient is unconscious and restless. Abdominal reflex absent; patellar and plantar reflexes are diminished; pupils equal; involuntary bowel movements.

June 10, 9 p. m. Temperature 98.4°, pulse 108, respiration 20. Under chloroform anæsthesia 90 c.c. of opalescent spinal fluid withdrawn and *22.5 c.c. of antiserum injected.* Microscopical examination of the spinal fluid showed many leucocytes and extra- and intracellular diplococci.—12 a. m. Temperature 98.8°, pulse 124, respiration 20.

June 11. Temperature subnormal most of the day. Patient rested fairly well latter part of night. Twitching of face and mouth; head retracted; rational at times.

June 12. Temperature subnormal. Mental condition greatly improved; abdominal and plantar reflexes present; patellar absent. Kernig's sign marked; neck rigid. Herpes appearing on lips. Complains of no pain unless moved.

June 13. Rested well during night.. Mental condition quite good; reflexes all present. Kernig's sign and neck rigidity unchanged. In nurse's absence has gotten out of bed and gone to closet. Temperature normal.

June 14. No change.

June 15. Condition good, all the reflexes normal. Almost no rigidity of the neck; Kernig's sign disappearing.

"From this date the patient continued to improve, and she finally made complete recovery. She left the hospital on June 23, thirteen days after admission, and has reported twice since."

Discussion.—The onset in this case was moderately severe, and the diagnosis of epidemic meningitis was established and a serum injection made within forty-eight hours of the appearance of the premonitory symptoms. The course of the disease was relatively mild, and the temperature tended to remain at the normal point or a little below it although the microscopical examination showed the presence in the spinal fluid of large numbers of *Diplococcus intracellularis.* A second lumbar puncture and serum injection were not made as the symptoms abated rapidly and the patient was convalescent on the fifth day of her illness. Total amount of antiserum injected, 22.5 cubic centimeters.

THE EPIDEMIC OF CEREBRO-SPINAL MENINGITIS AT CASTALIA, OHIO.[2]

The village of Castalia has a population of about 600 persons. Within the village nine cases of meningitis developed. In the outlying country and within three miles of the village, six cases developed. In the country adjacent to the village of Vickery, which is eight miles from Castalia, three cases developed. Thus a total of eighteen recognized cases of meningitis developed in this region between January and April, 1907. The first case appeared near Vickery in January and the remaining seventeen cases appeared between March 1 and April 2. Eleven of the eighteen cases were in adults over 16 years of age, and seven cases were in children between three and six years of age. Of the affected adults nine died and two recovered and of the affected children three died and four recovered.

In the past thirty years sporadic cases of the disease have appeared occasionally, but at long intervals. No case had been recognized previously for five years.

The distance between cases No. 1 and No. 2 was six miles; between No. 2 and No. 3, three miles, between No. 3 and No. 4 one mile. The first three cases occurred in the country. Case No. 4 appeared in Castalia and was followed in rapid succession by eight other cases. Only two of the cases had been in close personal relation with other persons affected.

At the time that Dr. L. W. Ladd brought the antimeningitis serum to Castalia there had been twelve deaths from epidemic meningitis and three cases were convalescent. He employed the serum on three cases as follows:[3]

CASE I. B. K. Female, aged 16 years. Patient of Dr. Storey.

Previously healthy girl. Taken ill suddenly March 30, 1907, with headache, vomiting and flushed face. The temperature was 104° F., pulse 124, respirations 48. Coma supervened within 12 hours. The diagnosis was made day after onset, at which time there were opisthotonos and rigidity of the extremities and petechial eruption of neck, trunk and thighs. The patient remained in coma until 12 a. m. March 31, when she became conscious. April 2 again became unconscious. Dr.

[2] Abstracted from the account of Dr. William Storey, published in the *Ohio State Medical Journal* for June, 1907.

[3] The histories of these three cases are taken from Dr. Storey's report and Dr. Ladd's notes.

Ladd first saw the patient at 7 p. m. April 2. At this time she was semi-conscious, the temperature was 103° F., pulse 120, respirations 48. Lumbar puncture was made, about 45 c.c. of very turbid spinal fluid were obtained and *5 c.c. of the antiserum injected.* The spinal fluid yielded *Diplococcus intracellularis* on coverslips and in cultures on sheep-serum glucose agar. April 3. Temperature 98.5°, pulse 108. Patient quite rational at times, though when not aroused she was delirious.—3 p. m. Temperature 101°; 11 p. m. 103.5°. Second lumbar puncture made, 30 c.c. turbid fluid withdrawn and *10 c.c. of antiserum injected.* The patient remained in a semi-conscious condition for 15 hours when the mental condition cleared; the opisthotonos and rigidity were noted to be much less marked. April 4. Acute bronchitis and broncho-pneumonia developed. The mental condition remained good and the meningeal symptoms were not prominent until April 18, when another puncture was made. About 50 c.c. of turbid fluid were removed and *10 c.c. of antiserum injected.* From this time improvement was gradual but steady. April 24, temperature normal; did not rise again. May 3, slight degree of foot-drop on left side. August 31, recovery complete.

Discussion.—The onset in this case was sharp and the course severe. Withdrawal of spinal fluid and injection of antiserum were made on the third day of illness. A favorable response seemed to follow. Two subsequent lumbar punctures and antiserum injections were made on the fourth and fifteenth day of illness. Following the second injection of serum the mental condition cleared and the rigidity of the body was noted as being diminished. The last injection was succeeded by gradual subsidence of all the symptoms and eventual complete recovery. The meningitis was complicated with an intercurrent broncho-pneumonia. Total amount of serum injected, 25 cubic centimeters.

Case II. F. W. Three years of age. Patient of Dr. Gorsuch.

This child was seen by Dr. Ladd twelve days after the beginning of the symptoms. The onset, consisting of vomiting, convulsions, headache, opisthotonos and great irritability, was sudden. Temperature at onset 104°, pulse 135, respirations 40. The patient had improved somewhat, although there was still great irritability and marked opisthotonos; temperature from 101° to 102.5°. April 3, marked opisthotonos and Kernig's sign; temperature 102°. Lumbar puncture yielded 30 c.c. of moderately turbid fluid. *5 c.c. antiserum injected.* That night, for the first time during the illness, the parents were not aroused. April 4, child less irritable; opisthotonos and rigidity less marked; food taken better. The temperature reached normal and remained so afterwards. April 28, child up and about. August 31, child well.

Discussion.—The abrupt change in the condition in this case was evidently associated with the withdrawal of spinal fluid and the

injection of the antiserum, but the part each played cannot be estimated separately. Total amount of serum injected, 5 cubic centimeters.

CASE III. J. B. Aged 23 years. Patient of Dr. Bowman. Employed on railroad.

Large man of excellent physique. On April 1 went to Freemont, Ohio, to a hotel. Asked to be called early April 2. The door of his room had to be forced open; the patient was found unconscious. He was removed to his home in Vickery and his physician called. On April 4 Dr. Bowman was convinced of the diagnosis of cerebro-spinal meningitis and sent to Castalia for Dr. Ladd.

Note by Dr. Ladd: Man of powerful build; comatose and restless: thrashing about the bed at times. Marked opisthotonos; purulent conjunctivitis; Kernig's sign present; petechial eruption and larger hæmorrhagic areas on body. Nose-bleed requiring packing to control. Temperature 103.5°, pulse 120, respirations 48 and stertorous. Lumbar puncture; 90 c.c. of turbid fluid removed; *10 c.c. of antiserum injected.* Regarded the condition as hopeless. April 5, in the morning patient still unconscious. Pulse was lower, temperature normal, respirations normal. In afternoon second puncture. 45 c.c. of less turbid fluid removed and *10 c.c. of antiserum injected.* April 6, *10 c.c. of antiserum injected.* Patient still unconscious. April 7, patient coming out of unconscious state. The progress was fluctuating and the patient was not without fever for 30 days. The improvement was gradual and the restoration complete. The patient returned to his work.

Discussion.—The case was one of abrupt and violent onset and of gradual subsidence of symptoms. The first puncture and injection of the serum were made on the fourth day of illness and were followed rapidly by improvement in the temperature, pulse and respirations. Two further injections of serum were given. The recovery was slow and complete. Total amount of serum injected, 30 cubic centimeters.

The epidemic of Castalia embraced 18 cases of meningitis of which 12 died and 6 recovered. Three of the latter recovered without lumbar puncture being performed and without the antiserum being injected. The three cases which were injected with the serum recovered. As these were the first cases in series to be injected with the serum the doses employed were smaller than the ones used subsequently.

The first case was injected with serum about 72 hours after the onset of the disease. Improvement was gradual and the symptoms subsided by lysis, hence it is not possible to assign certainly the

precise value of the serum injections. The second case, which was already in its second week of the disease, seems to offer more certain proof of the value of the puncture and serum injection. The disease terminated abruptly after the injection of 5 cubic centimeters of the serum and recovery was rapid and complete.

The third case was regarded as hopeless. Lumbar puncture and injection of antiserum having been made, the patient's condition changed quickly for the better, but the final recovery was fluctuating and gradual. The precise value of the serum injections must therefore remain doubtful.

EMPLOYMENT OF THE SERUM BY DR. L. W. LADD, OF CLEVELAND.

Dr. Ladd treated in all sixteen cases of epidemic meningitis in which the diplococcus was found with the antiserum in Castalia and Cleveland. He has kindly supplied us with the notes of his cases which will be presented in this place. Since three of the cases treated by Dr. Ladd were at Castalia the histories relating to them are given under the local epidemic of which they formed a part. We will first present Dr. Ladd's own analysis of the sixteen cases, then an analysis of our own, after which the case-histories of each to which we have added a brief discussion will be given.

"The sixteen cases consisted of 11 males and 5 females. Five patients were over 16 years, eight under 5 years and three between 5 and 8 years of age. When first seen thirteen of the sixteen cases were in coma, one was semi-comatose and two were conscious. Five patients were seen 24 hours or slightly earlier after the onset of symptoms. All these cases recovered completely. One patient was seen 48 hours after the onset. The condition was desperate. The patient died. Four patients were seen approximately 72 hours after the onset. They recovered. Two of these cases recovered completely, one developed foot-drop and recovered subsequently, one had impaired hearing when last seen. Three patients were seen approximately 96 hours after the onset. They died. Two of these cases showed a temporary improvement following lumbar puncture and serum injections. Two patients were seen two weeks after the onset, one recovered, the other died of chronic hydro-

cephalus. One patient was seen one month after onset and died of chronic hydrocephalus."

The percentage of recoveries among the sixteen cases was 68.75 and the deaths 31.75. Taking the ten cases treated with serum within 72 hours of the onset of symptoms, nine recovered and one died. The percentage of recoveries in this series is 90. Two of the five cases ending fatally were injected with the serum 96 hours or thereabouts after the onset and two cases several weeks after the beginning of the disease.

Case	I,	1st injection	on	3d	day;	total serum injection	25 c.c.;	recovery by	lysis.
"	II,	"	"	12th	"	"	5 c.c.;	"	crisis.
"	III,	"	"	4th	"	"	30 c.c.;	"	lysis.
"	IV,	"	"	5th	"	"	15 c.c.;	died.	
"	V,	"	"	2d	"	"	35 c.c.;	recovery by	crisis.
"	VI,	"	"	1st	"	"	15 c.c.;	"	"
"	VII,	"	"	3d	"	"	20 c.c.;	"	"
"	VIII,	"	"	3d	"	"	45 c.c.;	"	lysis.
"	IX,	"	"	2d	"	"	35 c.c.;	died.	
"	X,	"	"	1st	"	"	15 c.c.;	recovery by	crisis.
"	XI,	"	"	20th	"	"	25 c.c.;	died.	
"	XII,	"	"	4th	"	"	46 c.c.;	"	
"	XIII,	"	"	1st	"	"	45 c.c.;	recovery by	crisis.
"	XIV,	"	"	14th	"	"	28 c.c.;	"	lysis.
"	XV,	"	"	3d	"	"	53 c.c.;	"	"
"	XVI,	"	"	4th	"	"	41 c.c.;	died.	

Scrutinizing this table closely we find that of the 11 patients who recovered the disease terminated, after serum injection, by lysis in five and by crisis in six cases. It is somewhat noteworthy to find that a case of meningitis which has lasted twelve days without intermission of symptoms should terminate abruptly after a lumbar puncture and serum injection. But of the several important cases terminating abruptly by crises where the serum injections were made on the first to third day, the most significant is case XIII in which the injection was made about two hours after the first appearance of the meningeal symptoms with the result of immediately arresting the progress of the disease.

A second tabulation dealing with the cases in children under five years of age, owing to the high mortality of epidemic meningitis in infants will be given.

Case	II, Age	3 years;	recovered;	1st injection on	4th	day of illness.	
"	V, "	3 "	"	"	2d	"	"
"	VI, "	2 "	"	"	3d	"	"
"	X, "	2 "	"	"	1st	"	"
"	XI, "	1½ "	died	"	20th	"	"
"	XII, "	2 "	"	"	4th	"	"
"	XIV, "	1½ "	recovered	"	14th	"	"
"	XVI, "	under 5 "	died	"	4th	"	"

Of the eight cases of this tabulation five recovered and three died. The three deaths occurred in children who received the serum for the first time on the twentieth and the fourth day of the illness respectively. On the other hand two children who were first injected on the fourth day, and one child injected on the fourteenth day recovered. There is no proof that the course of the disease in the last case was essentially influenced by the antiserum.

CASE I. B. K. Castalia epidemic. Recovered.

CASE II. F. W. Castalia epidemic. Recovered.

CASE III. J. B. Castalia epidemic. Recovered.

CASE IV. H. White male, aged 17 years. Barberton, Ohio.

The patient was employed at the Goodrich Rubber Co.'s factory at Akron. May 2, in the evening, he complained of fever and headache. He was seen by Dr. Lahmers May 3. At that time there were diarrhœa and vomiting, but no fever. The same evening meningeal symptoms and coma came on. May 6 Dr. Ladd saw the patient. There were extreme opisthotonos—the head almost touched the scapulæ—general rigidity, Kernig's sign, petechiæ over body, and purulent conjunctivitis. Temperature 103.5°, pulse 85, respirations 30. Lumbar puncture yielded two or three drops of thick pus. *15 c.c. of antiserum were injected.* No beneficial effect was noted. Died May 7.

Discussion.—The character of the exudate in this case and the general condition of the patient five days after the beginning of the infection, probably operated against any beneficial effects resulting from the serum. Total amount of serum injected, 15 cubic centimeters.

CASE V. W. F. Male, aged 3 years. Bohemian.

On March 31 complained of headache in afternoon. April 1, severe headache; vomited. From 1 until 5 p. m. five convulsions, each lasting five minutes.—5 p. m. Coma, opisthotonos and Kernig's sign present; abdominal reflex absent; small petechiæ over body.—9 p. m. Lumbar puncture: 30 c.c. turbid spinal fluid removed and *10 c.c. of antiserum injected.* Temperature 99.4°, pulse 125, respirations 30.

April 2. Patient improved. Temperature and respiration unchanged, opisthotonos less marked, abdominal reflex present. Child conscious and rational; took nourishment.

April 6. Until to-day the child has done well. Temperature suddenly rose to 103.5°, pulse 116.

April 7. Lumbar puncture done in morning and 30 c.c. turbid fluid removed and *15 c.c. of serum injected.* The child was delirious before the puncture.

April 8. Temperature 99.6°, pulse 120.

April 22. Child did well until to-day, when the temperature rose to 103.2°; pulse 132. Vomiting and meningeal symptoms present. Lumbar puncture removed 30 c.c. of fluid; *10 c.c. of antiserum injected.*

April 24. Temperature normal. From this date on the recovery was uneventful and finally was complete.

Discussion.—The first lumbar puncture and serum injection were made within 48 hours of the onset of symptoms. The disease seemed to have been promptly arrested by the injection. Subsequently two relapses occurred, one on the sixth and the other on the twenty-second day, which were as abruptly arrested as the first symptoms by the lumbar puncture and serum injection. Recovery was complete. Total amounts of serum injected, 35 cubic centimeters.

CASE VI. Baby N. Female, aged 2 years. Italian.

Child lived in the poor district of Cleveland. Dr. Steuer, the attending physician, diagnosed the case as meningitis and called Dr. Ladd—22 hours after the onset of symptoms. Child had marked opisthotonos, lateral nystagmus, Kernig's and MacEwen's signs and muscular rigidity. She was completely comatose. Temperature 102.5°, pulse 140, respirations 40. Lumbar puncture: 50 c.c. of turbid fluid removed and *15 c.c. of antiserum injected.* Morning of next day, temperature, pulse and respirations normal; child dull and listless but conscious. Kernig's sign and opisthotonos less marked. Parents refused second puncture and injection of serum. The meningeal symptoms quickly subsided and recovery was complete. A few days later whooping cough developed, from which recovery was finally made.

Discussion.—The essential facts in this case are the sudden onset of severe symptoms of meningitis in an infant of two years and their abrupt arrest and permanent and rapid dissipation after lumbar puncture and serum injection performed in the first first twenty-four hours of the disease. Total amount of serum injected, 15 cubic centimeters.

CASE VII. X. Female, aged 11 years. American.

May 1. Patient seized with severe headache, vomiting, stiffness of neck. 12 hours later unconscious. Opisthotonos marked; Kernig's sign present; lateral nystagmus; petechial eruption. May 4 Dr. Ladd saw patient and did lumbar

puncture. 30 c.c. of turbid fluid removed and *10 c.c. of antiserum injected* (this within 72 hours of the onset of the symptoms). Temperature 103.6°.

May 2. Temperature and pulse normal; patient answered questions rationally though lapsed into semi-consciousness when left alone.

May 6. Improved.

May 7. Temperature rose and meningeal symptoms became prominent. Lumbar puncture repeated; *10 c.c. antiserum injected.* Temperature fell to normal. Complete recovery.

Discussion.—The prompt amelioration of the severe symptoms by the first lumbar puncture and serum injection and the equally prompt suppression by these means of what threatened to be a relapse of the disease, are striking incidents of this case. Total amount of serum injected, 20 cubic centimeters.

CASE VIII. W. H. White male, aged 21 years. Hudson, Ohio. Farmer.

May 12. Had a chill in evening. May 13. Unable to work.—8 a. m. Had a second chill and severe headache. In a few minutes was delirious and soon became unconscious. Dr. Ladd saw the patient May 14. There were present marked opisthotonos, Kernig's sign, general muscular rigidity and petechial eruption. (It developed that two weeks before the patient's mother had nursed a fatal case of epidemic meningitis.) Lumbar puncture was attempted four times but only a few drops of bloody serum were obtained. This fluid showed doubtful diplococci. The culture was negative. Clinically there was no doubt of the diagnosis. In view of the fact that no spinal fluid was obtained, *5 c.c. of antiserum* were injected into the canal and *10 c.c. antiserum under the skin.* Temperature 103.5°.

May 15. Patient improved; rational at times, opisthotonos, muscular rigidity and Kernig's sign less marked. *15 c.c. antiserum injected subcutaneously.* The temperature ranged from 100° to 103°, when, on the twelfth day, it fell to normal and remained there. On the seventh day of illness another dose of *15 c.c. of the antiserum* was given subcutaneously. A marked erythematous rash appeared on the fifteenth day. Recovery was complete.

Discussion.—The absence of bacteriological confirmation of the diagnosis in this case is an evident weakness, but there would appear to be little doubt of the nature of the disease. What is noteworthy is the subcutaneous employment of the antiserum. The symptoms gradually subsided by lysis and hence the special influence of the serum cannot be defined with certainty. Total amount of serum injected, 45 cubic centimeters.

CASE IX. C. G. White female, aged 6 years.

The patient was one of three children in one family afflicted with meningitis. June 30, at 4 a. m., was taken with headache and vomiting. July 1, at 10 a. m.,

had a convulsion. She was brought comatose to the City Hospital. There were marked Kernig's sign and opisthotonos. Extensive petechiæ and herpes oris. July 2, 8 p. m., lumbar puncture yielded 5 c.c. very turbid fluid. *10 c.c. of antiserum were injected.*

July 3, 10.30 a. m. Lumbar puncture done and 15 c.c. very turbid fluid removed. *10 c.c. antiserum injected intraspinally and 5 c.c. subcutaneously.*

July 4. Right-sided hemiplegia developed. Patient's condition still very bad.

July 5, 11 a. m. Lumbar puncture and administration of *10 c.c. antiserum.*—7 p. m. Condition very bad. Temperature 107.4°. Death. Consciousness never regained.

Discussion.—The onset of symptoms was in this case rapid and severe. The first lumbar puncture and serum injection were made about 64 hours after the first symptoms were noted, and while the patient was in an unconscious state. Two later injections of the serum were given, but no beneficial effect followed any of the injections. Total amount of serum injected, 35 cubic centimeters.

CASE X. J. C. White male, aged 2 years.

This is the second child having meningitis in this family. July 1, patient put to bed in good health. Later in the evening he was found restless and feverish. The physician made a diagnosis of meningitis. Admitted to City Hospital July 2, 9 a. m.

July 2. On admission marked opisthotonos, Kernig's sign and general petechial eruption were noted. Child comatose. At 4 p. m., approximately 20 hours after onset of symptoms, lumbar puncture performed and 50 c.c. of turbid fluid removed; *10 c.c. of antiserum injected into spinal canal and 5 c.c. under the skin.* Temperature at this time was 104°, pulse 140, respirations 62.—7 p. m. Temperature 105.6°, pulse 148, respirations 78.

July 3. This morning temperature 100°, pulse 128, respirations 40. Child conscious and irritable.

July 4, 10.30 a. m. Lumbar puncture negative (probably unsuccessful). The patient's condition quickly improved and, except for a slight rise of temperature to 102.4° at 12 a. m. July 5, the temperature, pulse and respirations remained normal.

July 17. No complications have developed. Child discharged cured.

Discussion.—The onset of symptoms in this case was sudden and severe. Twenty hours after the symptoms appeared lumbar puncture and serum injection were performed. Within twenty-four hours of these operations the condition had changed abruptly for the better and the disease had terminated by crisis. Recovery was uninterrupted. Total amount of serum injected, 15 cubic centimeters.

CASE XI. P. G. White male, aged 18 months. Austrian.

March 12. Admitted to Lakeside Hospital. Until March 4 the child had been well since birth. On that day was fretful and feverish, coughed and had diarrhœa. March 7, right elbow swollen and painful; neck stiff; macular eruption over body. On admission to Hospital there were irritability, large head retracted to right side, slight strabismus, pupils equal and active to light, slight swelling about flexed and rigid right elbow.

March 23. Temperature 105°. Lumbar puncture: 25 c.c. slightly turbid spinal fluid removed. On microscopical examination a small number of leucocytes containing diplococci of typical intracellularis appearance seen. No change in condition as result of puncture. Lumbar puncture every third or fourth day as routine. Temperature ranged from 98° (a. m.) to 104° (p. m.). No marked change in the physical condition.

April 12. Lumbar puncture and *intraspinal injection of 5 c.c. serum.*

April 14. Temperature did not rise above 100.5°, which was the lowest maximum temperature since admittance.

April 16, a. m. Temperature normal. *7 c.c. antiserum injected.* Temperature normal until April 23, when it rose suddenly to 104°, pulse 140, respiration 40. Symptoms of chronic hydrocephalus developed. Several additional punctures and injections of serum were made without beneficial effect. Death on July 30.

Discussion.—The first lumbar puncture was made on the twentieth day and the first serum injection was given on approximately the fortieth day of illness. Following the latter the symptoms diminished and there seemed decided improvement lasting eleven days. The symptoms reappeared and death resulted from chronic hydrocephalus. Total amount of serum injected, more than 25 cubic centimeters.

CASE XII. F. P. White male, aged 3 years.

Onset sudden on May 18 with headache, vomiting and temperature to 106.5°. Bright red pin-point rash over body. May 20, first convulsion noticed. Opisthotonos pronounced.

May 22 (about 96 hours after onset). Lumbar puncture and 45 c.c. of very turbid fluid withdrawn. Two hours later second puncture, 20 c.c. fluid removed and *15 c.c. antiserum injected.* Temperature 103°.

May 23. Patient brought to Lakeside Hospital. Temperature 101°, pulse 140, respirations 40. Conscious, very irritable, opisthotonos and Kernig's sign moderately marked (as on 22d, when seen by Dr. Ladd). Petechial eruption present.—4 p. m. Lumbar puncture: 50 c.c. turbid fluid withdrawn and *15 c.c. antiserum injected.*—12 a. m. Temperature 101.6°.

May 24. Patient drowsy; neck rigidity increased. 8 a. m. Temperature 102°. —3 p. m. Lumbar puncture: 40 c.c. turbid fluid removed and *16 c.c. serum injected.* Temperature 103.5°, pulse 135.—4 p. m. Chill, marked cyanosis, pulse feeble, respirations poor.—4 p. m. Temperature 106°. After tub bath temperature 104°.—9 p. m. Chill, cyanosis, temperature 106.5°. Death at 1.25 a. m., May 25.

Discussion.—The first lumbar puncture and serum injection were made 96 hours after the onset of symptoms, and on the next two successive days the punctures and injections were repeated. The disease progressed rapidly and continuously and ended fatally approximately six days after the onset. The question arises whether the sudden change for worse on May 24 bore any relation to the puncture and injection of serum one hour previously. There are no data at hand to use in answering this question. In other cases in which daily injections of serum were made severe symptoms did not appear. Total amount of serum injected, 46 cubic centimeters.

CASE XIII. O. C. White female, aged 7 years. Sister of F. C., Case XII.

Until May 21 child well. Symptoms began with fever (to 106°), severe headache, thirst and erythematous eruption over arms and legs. May 22, 2 p. m., child seen by Dr. Ladd.

May 22. Child conscious. No Kernig's sign. No opisthotonos, rigidity of neck or extremities. A bright erythematous eruption over chest and extremities. During the two hours which were employed in the examination of the fluid withdrawn from brother, marked meningeal symptoms developed, convulsions and opisthotonos and coma set in. Lumbar puncture was done, 30 c.c. of turbid fluid were withdrawn, and *15 c.c. of antiserum injected intraspinally.* The patient spent a quiet night and was brought to the Lakeside Hospital May 23.

May 23, a. m. Temperature 100°, pulse 120, respirations 35. Considerable restlessness. Moderate opisthotonos and rigidity of extremities. Unconscious. Kernig's sign present.—4 p. m. Lumbar puncture: 25 c.c. serum under moderate pressure removed and *15 c.c. serum injected.*

May 24. Condition greatly improved. Opisthotonos almost gone. Kernig's sign diminished, child less irritable and conscious though dull. Temperature normal, except for rise to 101.5° following puncture and injection of *15 c.c. of antiserum.* Only a few drops of turbid fluid obtained.

May 25. Temperature normal; mind clear; meningeal symptoms absent. Recovery uninterrupted. The disease in this case terminated in four days from its beginning.

Discussion.—The symptoms in this case set in abruptly and with much intensity. Within the first 24 hours of illness the diagnosis was established by lumbar puncture and the first serum injection made. What is especially important in this case is the fact that the puncture and serum injection were made in less than two hours after the appearance of symptoms due to meningeal irritation. The disease appears to have been arrested by the first puncture and

injection and, although two subsequent injections of serum were made, the symptoms disappeared rapidly after the first injection and the patient was well on the fourth day from the onset of the illness. Total amount of serum injected, 45 cubic centimeters.

CASE XIV. L. S. White male, aged 1 year and 7 months. Pole.

May 25. Admitted to Lakeside Hospital. Two weeks before the child fell while playing and lay for a few moments with head retracted. In a little while fell again in convulsion. On undressing him the mother noticed an eruption on the body. During the next five days the child had four convulsions; has been in bed since with head retracted and squint. On admission to hospital there were noted emaciation, marked opisthotonos and internal squint. Kernig's sign present. Lumbar puncture gave 25 c.c. turbid fluid. Temperature 101°, pulse 165, respirations 45. *5 c.c. antiserum injected.* Temperature normal during next four days.

May 28. Temperature 101.5°. Lumbar puncture gave 15 c.c. clearer fluid. *6 c.c. antiserum injected.* From the first puncture and injection the opisthotonos diminished and the mental condition brightened. Until June 1 temperature normal.

June 1, 12 a. m. Temperature 103.5°; next morning normal. Child gaining steadily in weight.

June 12. Temperature 103°. Lumbar puncture yielded 25 c.c. of clear spinal fluid in which a small number of diplococci were still present. *7 c.c. antiserum injected.* Until June 25 steady improvement.

June 25. Temperature 102°. *5 c.c. of serum given under the skin.* Temperature returned to normal but on June 27 again rose to 102°. *5 c.c. serum given subcutaneously.* No further rise occurred. Discharged cured.

Discussion.—This case is an example of sub-acute epidemic meningitis in which the symptoms rapidly ameliorated after lumbar punctures and serum injections began two weeks after onset of the disease. The only point that is especially noteworthy is the rapid clearing of the spinal fluid after the first puncture and serum injection. No statement of the precise part played by the serum can be made. Total amount of serum injected, 28 cubic centimeters.

CASE XV. C. D. White male, aged 8 years. German.

The patient was well until the night of June 13. Onset of disease was with irritability, severe headache and vomiting. June 16, diagnosis of meningitis made. There were present marked opisthotonos, muscular rigidity of extremities and petechial eruption. Patient comatose, respirations stertorous.

June 16, 1 p. m. Temperature 103°. Lumbar puncture gave 45 c.c. of turbid fluid; *10 c.c. antiserum injected.*—8 p. m. 45 c.c. spinal fluid removed and *5 c.c. antiserum injected.* The symptoms ameliorated somewhat during the day.

June 17. Temperature and pulse normal. Toward evening patient can be made to respond to loud questions but answers are unintelligible.

June 18, a. m. Temperature 104°; restless.—9.50 p. m. Lumbar puncture: 40 c.c. of turbid fluid withdrawn and *15 c.c. of antiserum injected.*

June 19, 12 a. m. Patient quiet, temperature normal. Mental condition clearer, temperature not above 101.5° for two days.

June 21. Restlessness; temperature 104°. Lumbar puncture: no fluid obtained, *5 c.c. antiserum injected under the skin.*

June 22. Temperature normal.

June 25. *5 c.c. serum subcutaneously.*

June 26, 12 a. m. Temperature 103°.

June 27, 8 a. m. *5 c.c. serum subcutaneously.* Temperature remained below 102° until June 30, when it rose suddenly to 104°.

June 30 to July 8. Up and down temperature.

July 8. Owing to increased irritability and symptoms of meningeal irritation lumbar puncture made and 35 c.c. of nearly clear fluid withdrawn.

July 10. After two days of nearly normal temperature there was a rise to 105.8°. Lumbar puncture made and *8 c.c. antiserum injected.*

July 11. Temperature normal. No further rise from this time. Patient discharged on July 29 well except for slight impairment of hearing.

Discussion.—The first puncture and serum injection were made on the third day of the disease and were followed by improvement in the patient's condition. The course of the illness was fluctuating and the symptoms subsided gradually and with occasional exacerbations. The lumbar punctures and serum injections, made during the access of the symptoms, appeared to control the fever and reduce the restlessness, while the subcutaneous injections of the serum would appear to have been less effective in this respect. Recovery was incomplete as impairment in hearing remained. Total amount of serum injected, 53 cubic centimeters.

CASE XVI. I. L. White, aged under 5 years. Hebrew.

June 18. Until to-day well. Complains of headache. June 19. Severe headache, vomiting, opisthotonos, petechial spots on body. In the evening unconscious. June 22. Admitted to Hospital (approximately 96 hours after onset). Symptoms unchanged except for exophthalmos on the right side and a lateral nystagmus. Lumbar puncture yielded 30 c.c. of very turbid fluid. *6 c.c. of antiserum injected.* Temperature fell from 104° to 100° in four hours; muscles less rigid; mind clearer.

June 23, a. m. Spinal puncture: 30 c.c. fluid removed and *5 c.c. serum injected.*

June 24, 4 p. m. Spinal puncture: 35 c.c. fluid removed and *5 c.c. serum injected.*

June 25. *5 c.c. serum given subcutaneously.* Following this the temperature which had ranged from 104.5° to 100° fell to normal.

June 27, 8 a. m. Temperature rose to 103°. Lumbar puncture, 2.5 c.c. reddish serum obtained and *5 c.c. serum injected.* Until July 9 child seemed to improve. The opisthotonos had diminished; temperature slightly elevated, sometimes reaching 104°.

July 9. Lumbar puncture: 45 c.c. of fluid removed and *5 c.c. of antiserum injected.*

July 13. 37 c.c. fluid withdrawn by puncture and *10 c.c. serum injected.* The temperature remained fluctuant; symptoms of increasing hydrocephalus developed and punctures and serum injections were repeated, but death took place on July 31, 1907.

Discussion.—This child was first injected with serum on the fourth day of the illness after which the acute symptoms ameliorated somewhat. The progress of the disease was not arrested by the several punctures and serum injections and chronic hydrocephalus and death resulted. Total amount of serum injected exceeded 41 cubic centimeters.

THE CASES OF EPIDEMIC MENINGITIS AT PHILADELPHIA.

The cases of meningitis at Philadelphia followed on the heels of the large epidemic at New York and probably constituted part of that epidemic. The report of the use of the antiserum at the Pennsylvania Hospital, supplied by Dr. Longcope, embraces five cases of the disease. Of these, four recovered and one died. We will tabulate these cases according to the period of the first injection of the serum, the total amount of antiserum employed in each case, and the mode of termination of the disease.

Case	I,	1st injection on	4th	day;	total serum injection	15 c.c.;	recovery by	crisis.
"	II,	"	"	3d	"	"	"	25 c.c.;	"	lysis.
"	III,	"	"	4th	"	"	"	45 c.c.;	"	crisis.
"	IV,	"	"	11th	"	"	"	25 c.c.;	death.	
"	V,	"	"	10th	"	"	"	15 c.c.;	recovery by	lysis.

Pennsylvania Hospital, Philadelphia. Service of Dr. M. J. Lewis.

CASE I. J. J. Negro male, aged 23 years. Stevedore.

Present Illness.—On the morning of July 2, 1907, the patient experienced headache, indigestion, weakness and exhaustion and pain in the back. During the afternoon the headache increased in severity, and a sense of malaise and illness was felt. He was brought to the receiving ward by the patrol service and remained over night. The next morning, as he felt better, he left the hospital and went to the wharf and lay down. Soon afterwards he became nauseated and vomited freely. The pain in the head returned with increased severity and there were pain and stiffness of the back of the neck, chilly and feverish sensations and

general pain of the body. That night (July 3) the patient went home and to bed and in spite of being very ill he went to work the next day. Later he was found unconscious on the wharf and was brought to the hospital (July 4). The note on admission states that the patient is unconscious, the neck is rigid, the urine is voided involuntarily, the temperature is 101° F., the pulse 80, and the respirations 26.

Physical Examination.—Large, robust negro lying unconscious but restless; irrational and somewhat noisy. Skin hot and dry; no rash; pupils react equally to light; slight degree of nystagmus and strabismus; conjunctivæ injected; tongue moist and heavily coated; breath offensive; moderate degree of rigidity; Kernig's sign present; patellar reflexes practically absent; sensations appear to be normal. (Nothing abnormal was discovered in heart, lungs and abdomen.) The urine showed a faint trace of albumen and a small number of hyaline and granular casts and leucocytes, but no sugar.

July 5. The alterations since yesterday are increased rigidity of neck and more marked Kernig's sign. Leucocyte count 15,800.—1 p. m. Lumbar puncture: 20 c.c. of very turbid fluid showing many *Diplococcus intracellularis* and pus cells obtained.—5 p. m. Second puncture: 65 c.c. fluid evacuated and *15 c.c. antimeningitis serum injected.* Temperature 100° F.—6 p. m. Temperature 102.2°, respirations increased, some degree of relaxation, patient quieter and less delirious apparently.—6.30 p. m. Temperature 101°, pulse 96, respirations 32.—9 p. m. Temperature 99.3°, pulse and respiration improved, patient more relaxed and has been perspiring, pupils react to light.—10.40 p. m. Partly rational and can be aroused sufficiently to give name, address and occupation; relaxation still more marked; headache is complained of.

July 6. Condition improved. Temperature 98.3°, pulse 60, respiration 20. Neck slightly rigid only, Kernig's sign greatly diminished; pupils equal and react; conjunctivæ clear; nystagmus and strabismus diminished; patient quiet and rational but is drowsy and somewhat stuporous. The next note reads: "This evening the temperature has gone up again; otherwise the general condition is much improved."

July 7. Temperature normal; condition improved; symptoms abating; headache, strabismus and muscular rigidity less marked; some diplopia present. Bowels moved freely.

July 8. Temperature 100°, otherwise no important change.

July 9. The note reads: "Temperature, pulse and respiration are normal. The patient is much brighter, headache has almost disappeared, the body is almost perfectly relaxed, patellar reflexes are normal, there is only a faint suggestion of Kernig's sign, the diplopia is less marked, but there is strabismus and paralysis of the left external rectus. The bowels have moved and the patient complains of hunger."

July 10. The urine contains a trace of albumen but no casts. Leucocytes 7.160.

July 11. Condition good, no discoverable rigidity, no headache, patient bright and hungry, tongue clean, temperature normal. Allowed to sit up.

July 12. All the symptoms except paralysis of external rectus and slight degree of diplopia have subsided; a suggestion of Kernig's sign remains. The diet is increased and the patient is allowed out of bed for a few minutes.

July 15. About ward.

July 18. Diplopia and Kernig's sign seem to be disappearing; still some paralysis of external rectus.

July 21. Feels well; can read without difficulty. No headache.

July 24. Improvement continues, paralysis of external rectus diminishing; all other symptoms have subsided.

July 26. "Discharged cured."

Discussion.—The first symptoms of meningitis appeared on July 2, and it is probable that lumbar punctures made at that time might have developed the nature of the disease. The symptoms increased in severity progressively until July 4 when they became marked. In view of the almost unavoidable uncertainty attaching to a determination of the onset of the disease it is safe to count July 3 to 4 as the first twenty-four hour period of its actual existence. Hence the serum was injected about 48 hours after the development of unmistakable symptoms. The symptoms abated rapidly after the second lumbar puncture and the injection of serum, and the patient experienced no relapses but improved progressively and made a complete recovery. Total amount of serum injected, 15 cubic centimeters.

Pennsylvania Hospital, Philadelphia. Service of Dr. J. C. Wilson.

CASE II. R. B. White male, aged 17 years. Clerk.

Present Illness.—On June 27, 1907, the patient was brought to the hospital in ambulance. He complained of malaise, severe headache, vomiting and constipation. The illness began on June 25 with malaise and headache. The same night the symptoms became suddenly much worse: headache, severe aches and pains of body, nausea and vomiting, chilly and feverish sensations, and alternating delirious and lucid periods until morning. The symptoms continued the next day and rigidity of neck was complained of. On admission temperature 100°, pulse 100, respirations 28.

Physical Examination.—Well-developed, robust-looking boy. Lies quietly in bed, although he tends to be restless and irritable; is rational but stuporous. Skin dry and hot; no rash; no herpes; face flushed; pupils slightly dilated and equal; react; conjunctivæ clear; tongue heavily coated and dry; head slightly retracted and rigid and painful. Kernig's sign marked; suggestion of Babinski reflex; patellar reflexes practically absent; some cutaneous hyperæsthesia; leucocytes 16,500 (nothing abnormal was discovered in heart, lungs and abdomen).

June 28. Condition essentially unchanged. The head is held more rigidly possibly and much headache is complained of.

June 29. Herpes appeared on lips; lumbar puncture at 3 p. m. and moderately turbid fluid obtained. *10 c.c. of antimeningitis serum injected* slowly into canal. No microorganisms found in the spinal fluid. One hour after the injection the temperature dropped from 100.6° to normal, the pulse became softer and ranged

from 74 to 64; respirations unchanged. Rigidity unchanged. In the evening temperature rose to 99.6°; patient very restless; morphia administered hypodermically.

June 30. Temperature 100.4°, dropping later to 98.4°; patient somewhat more comfortable; pulse 72. Evening: patient seems better, less pain and rigidity of head; has been sleeping or dozing much of the time; takes nourishment; bowels freely opened. Leucocytes 15,800.

July 1, 4.30 p. m. Lumbar puncture and 80 c.c. fluid removed; *15 c.c. antimeningitis serum injected.*—7 p. m. Temperature has risen from 98.5° to 101.5°. Patient perspired freely. No microorganisms found on cover-slips but many leucocytes. One colony of Gram-negative diplococcus grew on calf-serum agar.

July 2. Kernig's sign present; pain in back and legs; no headache; rigidity of head diminished. Leucocytes 10,550.

July 3. Has been very comfortable; no morphia given since July 1; no headache; rigidity of neck much lessened so that the head can be brought pretty well forward. Kernig's sign much diminished; no bodily discomfort; temperature normal or slightly subnormal.

July 4. Quite comfortable; hungry; given ice cream and orange juice. Kernig's sign diminishing.

July 6. Slight evidence of Kernig's sign; comfortable; on soft diet.

July 9. Up on bed rest.

July 16. Stiffness and pain in neck entirely and Kernig's sign practically gone. Temperature subnormal. Discharged.

Discussion.—The disease in this case began, probably, on June 25, the symptoms growing severe within 24 hours of their first appearance. The diagnosis of epidemic meningitis is rendered probable but not certain by the bacteriological examination. Lumbar puncture was performed and anti-meningitis serum injected twice. The first injection was made on approximately the third day, and the second on the sixth day of the disease. The recovery of the patient was progressive and complete without relapses.

Pennsylvania Hospital, Philadelphia. Service of Dr. Newlin.

CASE III. A. G. White female, aged 15 years. Canvas weaver.

Present History.—Went to work on September 6, but came home at noon on account of pain in head and back of neck. September 7 and 8 vomited several times. Since 6th inst. has been delirious and feverish and crying out. Admitted to hospital September 8.

Physical Examination.—Well-developed young girl lying in bed with chin thrown up and neck held stiffly; eyes injected; pupils equal, react; tongue heavily coated, dry; herpes about mouth; crying out; no rash. Kernig's sign well marked; knee jerks present, no ankle clonus. Nothing abnormal discovered in heart, lungs and abdomen.

September 9. Lumbar puncture yielded 3 c.c. of very turbid fluid containing *diplococcus intracellularis.* Leucocytes 23,000.

September 10. Condition unimproved. Kernig's sign and rigidity of neck more marked. Patient delirious, but can be made to give rational answers to questions.

September 11. Leucocytes 12,200. 50 c.c. of turbid, white fluid containing meningitis cocci withdrawn by lumbar puncture and *15 c.c. antimeningitis serum injected* into the spinal canal.

September 12. The note reads: "Twelve hours after the puncture and injection of the serum the temperature came down by crisis from 102.5° to 97° F.; the patient was quiet and sleeping soundly. The pulse was good and the respirations slow and regular. This morning the rigidity of the neck is lessened, the headache is less, the temperature subnormal, the respirations are regular and slow, the pulse slower (84) and of good volume, and the patient is improved in every way. The pupils are moderately dilated and the movements of the eyes good. There is a marked herpetic eruption about the mouth and three ulcers; one between fingers on the left hand and one on the left ear, and another beginning beneath the left eye. Leucocytes 8,750. "While counting the leucocytes six diplococci were found in a broken polymorphonuclear cell" (note by Dr. Longcope).

September 13. The temperature rose again yesterday, but came down during the night. This morning obtained 30 c.c. fluid by lumbar puncture and injected *15 c.c. antimeningitis serum.*

September 14. Much better to-day. Rigidity of neck and Kernig's sign almost gone; temperature subnormal; is rational.

September 15. Improving, but paralysis of the left external rectus is noted.

September 16. The paralysis of external rectus more noticeable and slight rigidity of neck and Kernig's sign still persist. 35 c.c. of clear, colorless fluid containing a few whitish flakes but showing no diplococci were obtained on lumbar puncture. *15 c.c. of antimeningitis serum injected.* Leucocytes 8,800. In the evening the temperature rose to 101°, the rate of respiration increased somewhat, but the pulse continued good (108). The rigidity of the neck and Kernig's sign were both increased, but they were much less marked than on admission.

September 18. Condition much improved. Neck rigidity and Kernig's sign have disappeared. Patient is hungry.

September 20. Temperature normal for three days.

September 24. Improving daily; house diet.

September 26. Out of bed.

September 30, discharged cured.

Discussion.—The onset of the disease in this case was abrupt, and the patient was admitted to the hospital about 48 hours after the appearance of symptoms. The diagnosis was established by the clinical symptoms and by lumbar puncture and a bacteriological examination on the third day of the disease, and a second puncture and an injection of the serum were made on the fourth day of the disease. It is worth noting that the circulating leucocytes fell to

one half the number between the first two punctures. A critical fall in the temperature took place after the second puncture and the first injection of the serum, and the general condition of the patient changed for the better while the rigidity of the neck muscles diminished. As the temperature rose slightly 72 hours after the first injection of serum a second puncture and serum injection were made. No further rise in temperature is recorded following the second injection of the serum. But as Kernig's sign and stiffness of the neck still persisted on September 16 and paralysis of the left external rectus appeared on the 15th, a third puncture and injection of serum were carried out. Since the leucocyte count was 8,800 on the day of the last injection complete previous cessation of active inflammation may be assumed, and the assumption is rendered certain by the limpid character of the spinal fluid withdrawn, from which all diplococci had disappeared. Forty-eight hours after the third puncture and serum injection all symptoms had subsided. The patient made a rapid and complete recovery.

Pennsylvania Hospital, Philadelphia. Service of Dr. Alfred Stengel.

CASE IV. C. B. White male, aged 11 years. Italian.

Present Illness.—The patient was admitted to the hospital on October 1 and had been sick since September 21. The onset was accompanied by vomiting, fever and chills. The complaint is of headache and pain in the back of the neck; the patient is delirious.

Physical Examination.—Half-grown, fairly well-nourished boy. He is very restless, requiring to be strapped in bed, and he cries out in delirium. Eyeballs are prominent; herpetic eruption about nose and mouth; tongue rough and covered with a brownish coat. The head is retracted and efforts to move it forward cause him to cry out. Suggestive Kernig sign; knee jerks unsatisfactory. Temperature on admission 101.2° F.

October 1. Leucocytes 10,500. 3 p. m. Lumbar puncture unsuccessful.—12.30 a. m. Second futile attempt to secure fluid by lumbar puncture. Patient very restless. Chloral and sodium bromide administered but ineffectual. Fairly quiet for 5 or 6 hours after ethyl chloride.

October 2, 4 p. m. Lumbar puncture yielded 6 c.c. thick, viscid, yellow pus. The last amount withdrawn thinner than the first. *10 c.c. of antimeningitis serum injected.* Pus contains many meningitis cocci. Kernig's sign positive. Patient very restless; muscular twitchings.

October 3. Leucocytes twenty hours after puncture 14,750. No relief from puncture and serum. Three hours after puncture temperature rose from 101° to 104° F. It remained at 104°, except for a temporary drop to 102° through the night and the next morning. Marked nystagmus this morning. Pulse weak and rapid (130–160), respiratory rate has been steadily increasing; muscular

twitchings are very marked and the arms are jerked spasmodically. Stimulation increased, but pulse and respiration grow steadily more rapid and feeble.—4 p. m. Lumbar puncture yielded 12 c.c. turbid, purulent fluid. *15 c.c. of antimeningitis serum injected.* Pulse and respiration gradually increasing. Temperature at 8.15, 106°. Unconscious and less noisy in delirium. Died at 1.45 a. m. (October 4). The autopsy (Dr. W. T. Longcope) showed acute cerebro-spinal leptomeningitis, acute broncho-pneumonia; chronic interstitial hepatitis; chronic interstitial splenitis; chronic fibrous pleurisy; congestion of intestine and hyperplasia of lymphoid follicles; and cloudy swelling of the kidneys.

Discussion.—The patient was admitted to the hospital on the tenth day of the disease. The puncture of the spinal canal indicated, and the autopsy proved, the cerebro-spinal meninges to be covered with a thick layer of pus cells and fibrin. No favorable influence was exercised on the course of the disease by the puncture and the serum injection carried out first on the eleventh and next on the twelfth day of the disease when the patient was already in an extreme condition.

Pennsylvania Hospital, Philadelphia. Service of Dr. Henry.

CASE V. P. C. Male, aged 18 years. Italian. Shoemaker.

Present Illness.—Patient came to the hospital on August 7 complaining of malaise, severe headache, chilliness and fever, nausea and constipation. The headache and malaise began on August 4 and increased so that he was compelled to stay in bed. On admission to the hospital the temperature was 101°, pulse 72, respirations 24.

Physical Examination.—Patient is moderately well-developed. He lies quietly in bed but is stuporous. Skin dry and hot; no rashes. Somewhat flushed and apathetic facies. Pupils equal and react sluggishly. Conjunctivæ injected. Tongue heavily coated and moist; breath fetid. The patient resents disturbance and becomes irritable; complains of pain in the head. (Nothing abnormal discovered in heart, lungs and abdomen. A blood examination showed Widal test negative and leucocytes 18,700. Slight degree of Kernig's sign present. Urine: no albumen, sugar or casts.

August 9. Temperature has almost reached normal; headache severe; there is marked rigidity of neck with slight retraction of the head. Some degree of rigidity of the back. The reflexes are exaggerated. Lumbar puncture was made at 1 p. m. but no fluid was obtained.

August 10. Temperature has risen. The condition of patient apparently worse; the stupor has increased and at times there is delirium. Rigidity of neck and Kernig's sign have increased; slight degree of nystagmus and strabismus. Lumbar puncture at 1 p. m. yielded 3 c.c. of spinal fluid tinged with blood. The centrifugated specimen showed polymorphonuclear leucocytes and red corpuscles, but no bacteria. Cultures were negative.

August 12. Condition essentially unchanged. The temperature fluctuated somewhat. Complains less of headache. Leucocytes 19,750. Lumbar puncture

at 1 p. m. yielded 4 c.c. of fluid of which 3 c.c. collected in one tube was slightly blood-tinged and 1 c.c. in another presented a silvery sheen. Cover-glass preparations showed many polynuclear cells, a few mononuclear cells and many red corpuscles, but neither tubercle bacilli nor diplococci. Cultures were sterile.

August 15. Patient slightly improved; brighter; temperature lower; still has considerable headache; persistence of neck rigidity and Kernig's sign; patellar reflexes exaggerated. Pulse good.

August 16. Condition about the same except that the temperature has become normal: Lumbar puncture at 1 p. m. yielded 7 c.c. of turbid spinal fluid. No tubercle bacilli found, but many pus cells and extracellular and smaller number of intracellular diplococci resembling the intracellularis, were seen. At 2.45 p. m. *15 c.c. of antimeningitis serum injected into the spinal canal.* "Patient stood the ordeal well, one hour later felt more comfortable and was dozing."

August 17. Temperature remains normal. Patient feels much better; he is brighter; headache less severe; neck less rigid, relaxing; Kernig's sign diminished.

August 19. Patient Convalescing. Headache slight; rigidity less; appetite improved.

August 22. Condition good; no headache; no rigidity; reflexes normal. Sitting up.

August 30. Discharged cured.

Discussion.—The diagnosis in this case must be accepted chiefly, if not entirely, upon the basis of the symptoms. The bacteriological examination of the fluid yielded by lumbar punctures does not supply convincing proof of the existence of epidemic meningitis. The degree of general leucocytosis is in agreement with what is commonly found in epidemic meningitis, but the evidence supplied by the leucocyte count is circumstantial. The examination of the sediment obtained from the spinal fluid showed an excess of polymorphonuclear cells, but it was not until the 16th instant, or on the tenth to twelfth day of the disease, that turbid spinal fluid, containing many leucocytes and stainable diplococci, was secured. It does not appear in the report that the cocci were certainly identified as *Diplococcus intracellularis* by culture tests. Hence the question remains open whether in this case the general cerebro-spinal fluid remained free of the diplococcus although an exudative inflammation of some extent existed in the membranes. The case appears to have been progressing towards recovery before the injection of the serum on the tenth to twelfth day of illness, and there is lacking all certain evidence that the progress in this direction was accelerated appreciably by the serum. Total amount of serum injected, 15 cubic centimeters.

RESULT OF THE USE OF ANTISERUM BY DR. CUSHING, OF BALTIMORE.

Dr. Cushing wrote one of us (Flexner) as follows:

"I remember your telling me that you thought there was very little chance of benefit to be expected from the serum in other than the acute stages of epidemic meningitis. It may, therefore, interest you to know of this single experience. A woman, aged 36 years, had a severe attack of cerebro-spinal fever with sudden onset, May 16, 1907. She was very ill and during the next few weeks Futcher and a number of others saw her in consultation. The condition dragged on until July, when I was asked to see her in the hope that there might be some prospect of operative relief, since she was still suffering from irregular periods of fever (103°–104°) during which there were marked stupor, severe headache, and cervical retraction. She had been ill in all about eight weeks. Though under the impression that there was some mechanical obstruction with hydrops ventriculorum, a lumbar puncture during one of her stuporous periods evacuated a large amount of not particularly turbid fluid which was under high tension. To my astonishment the fluid was swarming with *Diplococcus intracellularis,* both inside and outside of cells. Forty-eight hours later, on the return of the stupor, another puncture was made and *15 c.c. of antimeningitis serum* were introduced into the spinal canal; the diplococci were still numerous. The temperature dropped to normal soon after. After a second forty-eight hours *this was repeated*; diplococci were few. Again in forty-eight hours there was a repetition of the puncture and *serum injection*; practically no diplococci could be found in the fluid, though there may have been a few organisms present. From this time on there were no further symptoms—no headache and no fever. She rapidly convalesced and has recovered her usual health."

Discussion.—The instructive points of this case relate to the persistence of the diplococcus in large numbers in the cerebro-spinal membranes for a number of weeks after the acute stage of the meningitis had passed off, and the action of the lumbar punctures and serum injections in interrupting and finally and quickly abating the free development of the diplococcus. Apparently the number of diplococci present at the second puncture, before any serum was injected, was not remarkably smaller than at the first puncture, while the next two notes describing the punctures and injections of serum dwell particularly on the diminution in numbers of the diplococcus. The subsidence of symptoms and return to perfect health were undoubtedly attendant upon and probably the outcome of the disappearance of the diplococcus from the cerebro-spinal membranes, and this disappearance was greatly aided by, and possibly accomplished through, the withdrawal of infected spinal fluid and the injection of the antiserum.

THE EPIDEMIC OF MENINGITIS IN GREAT BRITAIN.

A severe epidemic of cerebro-spinal meningitis, caused by *Diplococcus intracellularis,* prevailed in several cities in England, Scotland and Ireland during the winter of 1906–7, and is still prevailing in those countries. We have been fortunate in securing the co-operation in testing the antiserum of Dr. Claude Ker, of the City Hospital of Edinburgh, and of Dr. A. Gardner Robb, of the Belfast City Fever Hospital and the Belfast Union Fever Hospital, of Belfast. We have received preliminary reports, based on a small number of cases of meningitis treated with the antiserum, from these gentlemen which are given in this place. They will doubtless publish their experiences in full later, after a larger number of cases, treated with the antiserum, have come under their observation.

Dr. Ker writes under the date of September 17, 1907:

"Our experience with the serum has so far been limited to four cases. The first three have done well and seem now, after four and three weeks' treatment in hospital, to be out of danger. Our general impression here is that, although averagely acute cases, they have done most exceptionally well. One, however, I fear will be permanently deaf.

"The fourth case was fulminant with profuse hæmorrhages in the skin. It was admitted 18 hours from the onset and died about 24 hours from the onset. It was therefore hopeless, but I thought it just and right to give it the chance, and it had one dose of *30 c.c. of the serum,* which could hardly have had time to be effective. The other cases had about 120 c.c. on an average each. The only selection I am making is to treat cases which are less than a week old.

"By the way, my bacteriologist tells me that it is exceedingly difficult to get the diplococci to stain as usual the day after the first intraspinal injection. This has not been noticed so much with other serums. The germs are there of course and can be seen, but they must be modified in some way by the treatment, as they certainly lose their staining power."

Dr. Robb writes under the date of October 23, 1907:

"Since my return to duty on 1st September the opportunities of testing the serum have not been many, but the results in the cases receiving it have been remarkably satisfactory. I have only had four cases admitted to hospital quite early in the attack since that time.[4]

"The first case was a man of 22 who was 48 hours ill when admitted. He was wildly delirious with normal temperature, cyanosis and plentiful petechiæ. I considered his case practically hopeless from my former experience. I gave him

[4] In addition, two chronic cases of meningitis were treated, as appears from the latter part of the letter.

30 c.c. of the serum after drawing off 90 c.c. of turbid fluid in which the meningococcus was present. 36 hours later he was quite conscious and had no headache; his temperature rose to 101° F. and remained about that level for some days; he had very abundant herpes, but his symptoms rapidly improved. I repeated the *30 c.c. injections at intervals of 3 days,* giving 90 c.c. in all. He made a complete recovery. The remarkably sudden clearance of the mental symptoms and the complete disappearance of the headache were very striking, and as this has taken place in other cases treated with the serum, I think the serum must have the credit.

"The second acute case was a girl of 12 years with very severe attack admitted on the second day. This case was very severe, but the prognosis without serum would have been uncertain. The same good results followed with good recovery.

"The third case, a woman of 31, had been ill 10 days with very severe attack; high temperature, delirium, and very marked rigidity. My prognosis would have been bad, but she rapidly improved after the serum and is in a fair way to recovery now. She had 90 c.c.

"The fourth acute case, a man of 20, with maniacal delirium, came in two days ago. I gave him *30 c.c. of serum* immediately on admission—then 46 hours ill. The cerebro-spinal fluid was quite purulent even then. He died of heart failure some 9 hours after receiving the serum.

"Even more striking were the results in two chronic cases. One boy not doing well, who had continuous fever for 35 days, received *30 c.c. of the serum.* From that time on he made steady improvement, had no further headache and has made a complete recovery. Another case which I considered quite hopeless got 30 c.c. on the 25th, and again on the 32d day. He made steady improvement from the first dose and is now up. One young child, who was also hopeless, showed no improvement and died, but in this case thick, stringy pus was obtained. In the chronic cases no improvement had followed simple drawing off of fluid.

"I quite appreciate how dangerous it is to draw conclusions from a few cases, especially during a lull in the epidemic, but allowing for all that I am greatly impressed with the results in the cases I have had. I believe there has been little if any change in the virulence of the type here. The cessation of the headache in the chronic cases receiving serum and in whom it had been most troublesome was very striking; and the absence of headache in the acute cases after serum I have not seen in any other cases."

Discussion.—There could be no advantage gained in discussing these cases, since they are reported so very briefly. Attention may, however, be called properly to the effects of the serum injections in the two cases of the chronic disease described by Dr. Robb. They recall the similar effects of the serum injections made in the chronic case of epidemic meningitis described by Dr. Cushing, of Baltimore.

ST. VINCENT'S HOSPITAL CASES, NEW YORK CITY.

The antiserum was not available for use in the treatment of meningitis during the prevalence of the severe epidemic in New York City. Since it has been available only occasional sporadic cases of the disease have continued to appear, and many of these have entered hospitals late in the course of the disease. Hence our opportunities for testing the antiserum under conditions of personal observation have been very few. We have secured from Dr. Strain, of St. Vincent's Hospital, the records of three cases of meningitis in adults caused by *Diplococcus intracellularis* of which abstracts follow.

CASE I, No history of onset obtained; total serum injection 30 c.c.; death.
CASE II, 1st injection of serum on 4th day; total serum injection 30 c.c.; recovered by lysis.
CASE III, No history of onset obtained; total serum injection, 60 c.c.; recovered by lysis.

St. Vincent's Hospital, New York. Service of Dr. Lewis.

CASE I. A. C., aged 22 years. Greek.

Present Illness.—No history could be obtained. Admitted to hospital, April 23, 1907.

Physical Examination.—The patient is in a semi-comatose condition. Pupils unequal; right pupil does not react to light; left is dilated; no strabismus. Herpes on upper lip. Marked retraction of the head and stiffness and tenderness of neck. Reflexes absent from extremities; Kernig's sign present. Babinski reflex absent.

April 23. Patient is somnolent, pulse slow and of medium tension; general condition poor. Temperature ranged from 102°–100°.

April 24. Patient noisy, crying out. No remarkable change. Leucocytes 18,000.

April 25. General condition about the same. 15 c.c. of turbid spinal fluid obtained by lumbar puncture. Microscopical examination showed pus cells and *Diplococcus intracellularis.*

April 26. Condition worse; the pulse is rising gradually and the first heart sound is becoming weaker; capillary circulation very poor; cyanosis; cold extremities. Temperature 100°–103°; pulse 99–112; respirations 28–34.

April 27. Condition about as yesterday. 20 c.c. of turbid spinal fluid removed by lumbar puncture and *30 c.c. of antimeningitis serum injected.* Following this the temperature rose 1° and then gradually declined during the night to 99°, the patient's condition gradually becoming worse.

April 28. Condition very bad; pulse hardly perceptible; respiration accelerated; physical signs unchanged.

April 29. Lumbar puncture unsuccessful. Condition bad.

May 1. Death at 1 a. m.

Discussion.—The duration of the disease in this case is not known. The diagnosis of epidemic meningitis, which was suggested by the symptoms, was established by lumbar puncture on April 25, two days after admission to hospital. The second puncture and the first injection of the serum were made on April 27, four days after admission to the hospital and at a time when the patient's condition was already very poor and the circulation had begun to fail markedly. No improvement followed the puncture and injection, but the patient's condition gradually grew worse until his death on May 1, eight days after admission to the hospital, four days after the serum injection, and an unknown period after the onset of the disease. Total amount of serum injected, 30 cubic centimeters.

St. Vincent's Hospital, New York. Service of Dr. Lewis.

CASE II. C. L. Aged 22 years. Greek. Laborer.

Present Illness.—On May 7 (one day before admission to hospital) the patient was taken suddenly ill with sharp chill and intense headache. The neck became stiff, and slight movement greatly increased pain in head and neck. There were fever and photophobia.

Physical Examination.—Flushed face; anxious expression; injected conjunctivæ; photophobia; beginning herpes on nose and lips; tongue coated; breath fœtid. Neck stiff and head retracted. Kernig's sign marked; reflexes absent; skin hyperæsthesia.

May 8. Temperature 102°, pulse 90, respirations 24 on admission. Patient quiet, but complains of headache. Under ice cap slept much of the day.

May 9. Patient somnolent; cries out at times. Temperature ranged from 103.4° to 105°; pulse 80–94.

May 10. At 9 a. m. and 1 p. m. temperature 104°.—4 p. m., lumbar puncture yielded 35 c.c. of turbid fluid containing pus cells and large numbers of diplococci. Headache better; slept much of night.—5 a. m. Temperature 100°.

May 11, 4 p. m. Lumbar puncture; 30 c.c. spinal fluid withdrawn and *30 c.c. of antiserum injected.* During the night patient was very noisy and required sedatives (morphia and hyoscin) to give sleep.

May 12, 9 a. m. Temperature 104°; remained high all day. No marked change in the condition.

May 13, 5 a. m. Temperature 100°. Pulse slow and full; mental condition apathetic. Temperature did not rise above 101°. Involuntary bladder and bowel movements.

May 14. Condition improved; mental condition brighter. Patient follows with the eyes persons and objects about the room.

May 15. No marked change. Temperature ranged from 101.8° to 103°.

May 16. Condition better. Awake greater part of day; headache less; does not complain of pain in the neck.

May 17. Improvement continues; patient comfortable; mentally brighter; less rigidity of neck; appetite improved.

May 19. Temperature normal; neck rigidity and headache almost gone; patient bright and cheerful.

The improvement in the patient's condition continued and he was discharged cured on June 8.

The leucocyte count on three occasions gave 11,000, 15,000 and 14,000.

Discussion.—The onset of the symptoms in this case was sudden and by the end of the first twenty-four hour period the disease had reached full development. On the third day, counted from the appearance of the first symptoms, lumbar puncture was made and the diagnosis established by bacteriological examination. The temperature fell, the headache diminished, and the patient rested better than before. On the fourth day a second puncture was made and the antiserum was injected. No immediate favorable effect followed, but 60 hours later the condition had improved and there was a steady subsequent inprovement up to complete recovery. Convalescence may be said to have begun not later than the tenth day of the disease. Total amount of serum injected, 30 cubic centimeters.

St. Vincent's Hospital, New York. Service of Dr. Lewis.

CASE III. G. P. Aged 18 years. Greek. Clerk.

Present Illness.—No definite history obtainable. About a week before admission to hospital on May 18, 1907, he complained of headache and vomiting.

Physical Examination.—Face flushed and expresses pain; photophobia; pupils equal and react to light; tongue coated and dry; neck rigid and head retracted; a few petechial spots on thorax, abdomen and legs; reflexes exaggerated; no clonus or Babinski; Kernig's sign marked. May 18 the temperature rose from 98.5° to 103°; pulse 85; respirations 28.

May 19–28. The condition has not greatly altered. The mental condition dull, there is much headache and at times delirium requiring restraint. The temperature did not rise above 102.5° and ranged about 101°. Leucocytes 24,000.

May 27. Leucocytes 21,000.

May 29. Patient quiet and somnolent. By lumbar puncture about 50 c.c. of turbid fluid were obtained and *30 c.c. of antiserum injected.* Following the injection the patient was quiet and the temperature fell to 99°. Microscopical examination of spinal fluid showed pus cells and intra- and extracellular diplococci, which were cultivated.

May 30 and 31. Mental condition somewhat improved; no delirium.

June 1. External strabismus appeared, otherwise no change.

June 2. Mental condition clearer; patient answers questions. Temperature fluctuating.

June 4. Patient complains of pain in neck and is at times somewhat delirious. About 50 c.c. of spinal fluid removed by lumbar puncture and *30 c.c. antimeningitis serum injected*. The temperature fell from 103° to normal in twenty-four hours. Delirium subsided and patient looked brighter. He had involuntary defecation and micturition.

June 6. Leucocytes 20,000.

June 7. Patient noisy at night, requiring sedatives.

June 10. Pulse weak but responds to digitalin.

June 11. Neck rigidity lessened; patient fairly comfortable; photophobia and strabismus gone; diet increased; temperature normal.

June 15. Patient gradually getting stronger; mental condition good.

June 18. Improvement continues.

June 21. Patient noisy and delirious all day; temperature 99°. For the next two or three days he was delirious at times.

June 27. Patient rational all day and slept and ate well. Temperature 97°.

June 29. Patient sat up for the first time.

July 5. Walked a few steps; leucocytes 6,000.

July 20. Discharged cured.

Discussion.—It is impossible to determine accurately the duration of the disease before the patient entered the hospital. On the eleventh day after admission lumbar puncture was made and a serum injection was given. Following these the patient's mental condition improved somewhat, but three days later external strabismus appeared. On the seventeenth day of illness a second lumbar puncture and serum injection were made which were followed within twenty-four hours by a marked fall in temperature and an improvement in the patient's mental condition. The temperature remained about normal afterwards, although there reappeared off and on for a few days, during the convalescence, a state of temporary delirium, which did not interrupt the general course of improvements in the patient's condition. Recovery was complete. Whether the serum injections influenced favorably the progress of the disease in this case cannot be determined with certainty. Total amount of serum injection, 60 cubic centimeters.

MANNER OF ACTION AND OF EMPLOYING THE ANTISERUM.

The plan to administer the antiserum by direct inoculation into the spinal canal in human beings was based upon the observations made by one of us (Flexner) on the bactericidal effect of normal sera and sterile exudates upon *Diplococcus intracellularis in vitro,*

and upon the curative action of antidiplococcus sera in guinea-pigs and monkeys infected with the diplococcus, when brought into immediate relation with the focus of infection. In view of certain theoretical objections to the employment as curative agents of antisera developed for a microorganism whose toxic action is caused by endotoxin, Flexner dwelt on the encouraging circumstance that in epidemic meningitis the main pathological lesions can be brought directly under the influence of the antiserum by injecting the latter into the spinal canal; and he pointed out that while it is undoubtedly important to secure neutralization of the endotoxin yielded by the diplococcus on disintegration, the effect of restraint of growth and multiplication of the diplococcus may, at some period of the disease, be of even greater significance.[5] There is experimental evidence for the view that the antiserum possesses a certain antitoxic value since it can neutralize the toxic substances contained in autolysates of the diplococcus. But its power to bring about rapid suppression of the diplococcus in infected guinea-pigs and monkeys is considerable. In monkeys which have been injected with mixtures of emulsions of the diplococcus and immune serum simultaneously, or first with the emulsion and next with the immune serum, the diplococcus is caused rapidly to diminish in numbers and to be more abundantly taken up by leucocytes.[6] Since the facts at hand do not warrant us in concluding that any considerable multiplication of the diplococcus takes place in the experimental infections, the power of protection of the antiserum would appear to be dependent upon the restraint which it exercises over all multiplication and the increased tempo of phagocytic inclusion of the diplococcus which it brings about. It is probable that phagocytic digestion not only prevents further multiplication of the diplococcus but also that it detoxicates the endotoxin by reducing it to simpler and non-toxic or less toxic compounds. Still, in a few instances, in which the antiserum was injected into the spinal canal of monkeys infected with the diplococcus, the microorganisms disappeared without marked phagosis and more slowly than in the cases in which outpouring of

[5] *Jour. of Exper. Med.*, 1907, ix, 138.
[6] *Idem*, p. 169 *et seq.*

leucocytes was considerable. The control of the pathological conditions in these instances appeared to depend less upon the phagocytes than upon the spinal fluid reinforced by the antiserum; and as the symptoms of intoxication were less than would have been present had the antiserum not been injected, a degree of antitoxic power must be ascribed to the antiserum.

If we turn to our knowledge of the manner in which the antiserum acts in controlling or modifying the infection in human beings we find ourselves possessed of very few facts. The observation recorded by Dr. Cushing indicates that the antiserum has the property of bringing about rapid diminution in the number of diplococci present in the cerebro-spinal fluid. Dr. Ker observed rapid rise of the opsonic index for the diplococcus following upon an antiserum injection and a modification and reduction of the staining power of the diplococcus in film preparations prepared from the meningeal exudate obtained by lumbar puncture. Others have noted this reduction in number and change in the staining properties of the diplococcus after the serum injections.

We have had the opportunity to follow in two young children the immediate effects of the antiserum injections on the number, appearances and viability of the diplococcus in the cerebro-spinal fluid. One of the children was 18 months old and had been two weeks ill when first injected at the Babies Hospital in New York. The spinal fluid withdrawn before the serum injection was slightly turbid and showed a fair number of extracellular and a large number of intracellular, sharply-staining diplococci. Cultures were easily secured from this fluid on blood and sheep-serum agar media. A second puncture made twenty-four hours after an antiserum injection yielded a fluid of the same appearance as before, but no extracellular diplococci, or very few, were contained in it, and the number of intracellular diplococci was much reduced. All the diplococci were more or less changed; they were swollen or fragmented and stained diffusely. Cultures were now negative. A second antiserum injection was given and the next day the diplococci had undergone a still greater reduction in numbers and continued to stain feebly. No cultures could be obtained from this fluid or any subsequent fluid from this child, although several later punctures were made.

The second child was two years old and had been ill about five days when admitted to the Presbyterian Hospital in New York under Dr. Northrup. The first lumbar puncture yielded a sero-purulent fluid containing large numbers of diplococci outside and inside pus cells. Abundant cultures mere easily obtained. An injection of 15 cubic centimeters of antiserum was given and twenty-four hours later the lumbar puncture yielded a fluid in which a little blood obscured the color, but the pus cells and diplococci were diminished in numbers. The latter were now almost wholly inside cells and of irregular size and contour and weak staining power. A portion of the fluid was centrifugalized and the sediment used for preparing cultures which did not grow. Serum injection and lumbar puncture were repeated on two later occasions. The spinal fluid withdrawn was far less purulent than it had been, the diplococci became very few in number, and they did not again multiply on culture media otherwise favorably adapted for the growth of the diplococcus.

These observations, few in number as they are, go to show that the antiserum exerts a definite and injurious influence upon the diplococcus in the cerbro-spinal fluid through which its multiplication is restrained and it is rendered more subject, possibly, to phagocytic inclusion and digestion, at the same time that it is deprived of its capacity to grow outside the body on culture media.

We have given the following general instructions for the use of the serum:

The antiserum should be kept in a refrigerator until it is to be used, when it should be warmed to the body temperature before it is injected.

The antiserum is to be introduced directly into the spinal canal after the withdrawal of cerebro-spinal fluid by means of lumbar puncture.

The quantity of antiserum to be used at a single injection should not exceed, for the present, 30 cubic centimeters. It is desirable, although it would not appear to be essential, to withdraw from the spinal canal at least as much fluid as the amount of antiserum to be injected. The injection should be made slowly and carefully to avoid the production of symptoms due to increased pressure. This

precaution should be exercised especially where the quantity of cerebro-spinal fluid withdrawn is less than the amount of antiserum to be injected.

The injection of the antiserum should be repeated every twenty-four hours for three or four days or longer. Whether any advantage will be gained by more frequent or more numerous injections than here indiciated a wider experience must decide. As much as 120 cubic centimeters of the antiserum have been injected into the spinal canal in four days without causing unpleasant symptoms.

The evidence at hand indicates that the earlier in the course of the disease the injections are made the better the results. Hence should the film preparation prepared from the first fluid obtained by spinal puncture show Gram-negative diplococci, some of which are within leucocytes, an injection of the antiserum should be made immediately and without waiting for the result of culture tests. Should the diagnosis be left in doubt or the disease prove later to be of another nature than epidemic meningitis, no harm will have been done by the injection of the antiserum.

Although the best results have thus far been obtained where the antiserum has been injected early in the disease, yet the serum should be used in its later stages also until our knowledge governing the value of the serum becomes more precise. The indications at present are that it is useless to employ the serum in the very late stages of the disease in which chronic hydrocephalus is already developed.

Precise records of the manner of action of the antiserum upon the general symptoms of the disease and the local inflammation and the diplococcus should be kept. Information is greatly desired on the influence of the antiserum upon the number, appearances, growing properties, etc., of the diplococcus, upon the relation of the diplococcus to phagocytosis, and on the number and appearances of the leucocytes, before and after the antiserum injections. Counting the leucocytes in the circulating blood, before and after the injections, would help determine whether the antiserum tends to bring a greater number of leucocytes into the inflamed membranes, or whether it leaves the number unchanged or causes cessation of the emigration.

Until the antiserum is proven to be of value or of no value in the treatment of epidemic meningitis its manner of action should be carefully observed and recorded so that a definite decision may be reached as quickly as possible.

DOES ANAPHALAXIS OCCUR FROM REPEATED INJECTIONS OF THE SERUM?

That the human organism reacts more vigorously to second and subsequent injections of horse serum than to the first injection is shown by the reports of many instances in which these stronger effects were noted after administering diphtheria antitoxin. v. Pirquet and Shick[7] call this condition of greater reaction on the part of the animal organism "serum-disease." Wolf-Eisner[8] sees in this state of intensified effect or hypersensibility the fundamental pathological condition underlying the manner of reaction of the animal body to repeated injections of foreign proteids in general, including the bacterial endotoxines. Our precise knowledge of serum-hypersensibility—or anaphalaxis—is due to the impulse given the study of the subject by Theobald Smith and to the exact studies of Otto,[9] Rosenau and Anderson,[10] Besredka and Steinhardt,[11] Gay and Southard,[12] Lewis[13] and others. The particular fact that concerns us at this moment is whether a possible danger to the patient is to be feared from intraspinal injection at considerable intervals of a foreign serum. We know that the intensified effects in man of repeated serum injections under the skin causes discomfort but does not menace life. Besredka and Steinhardt have, however, shown that it is precisely the direct inoculation of the central nervous system with the alien serum in a hypersensitive guinea-pig that is to be feared. It is, therefore, of the first importance to us to ascertain whether a similar danger exists in relation to the intradural injection of the antimeningitis serum.

[7] Die Serumkrankheit, Vienna, 1905.
[8] *Berl. Klin. Woch.*, 1907, xliv, 38.
[9] *Leuthold-Gedenkschrift*, 1906, i, pt. 1, 153.
[10] *U. S. Marine Hosp. Service Hygiene Lab. Bull.*, 1906, No. 29.
[11] *Annales de l'Institut Pasteur*, 1907, xxi, 117, 384.
[12] *Jour. of Medical Research*, 1907, xi, 143.
[13] *Jour. of Exper. Med.*, this number.

There is no danger, apparently, to be apprehended from a single injection of even a considerable volume of the serum into the spinal canal. Daily intradural injection of the antiserum seem also to be well borne, at least, for several days. The question arises whether it is safe to give the injections at intervals of many days, since an interval is necessary in order that the reaction of hypersensibility shall be developed. Dr. Ladd's Case V, a child of three years, was injected on the following dates: April 1, 6, 22; no ill effects followed and recovery was complete. His Case XV, a child of eight years, was injected as follows: June 16 intradurally, June 18 idem, June 21 subcutaneously, June 25 idem, June 27 idem, July 10 intradurally; no ill effects followed and the child recovered. Still other instances of repeated injection, with intervening long interval between certain injections, will be found among the recorded cases. The danger does not, therefore, seem to be great.

We wish now to refer to an infant who was injected at the Babies Hospital, New York City, several times with the antiserum. The fourth injection was made 42 days after the first and 16 days after the third injection and was followed by convulsions, prolonged rigidity and elevation of temperature.

Babies Hospital, New York. Service of Dr. L. Emmett Holt.

E. F. Female child, 11 months old. About the middle of August developed fever, hyperæsthesia, rigidity and projectile vomiting. Admitted to Babies Hospital September 6, 1907. Lumbar punctures on September 7 and 11: turbid fluid withdrawn. September 12, 45 c.c. fluid withdrawn and *5 c.c. antiserum injected.* September 17, 25 c.c. fluid withdrawn, no injection. September 28, 7 c.c. fluid withdrawn and *7 c.c. antiserum injected.* October 8, 3 c.c. fluid withdrawn and *5 c.c. antiserum injected.* No symptoms developed following these injections. October 24, 60 c.c. fluid were withdrawn and *20 c.c. antiserum injected.* Previous to the last injection the child was relaxed and opisthotonos was absent. She was restless and irritable, vomited occasionally, cried if disturbed, and was apparently deaf. The reflexes were increased and there was marked emaciation. The antiserum was administered intradurally at 11 a. m. At 3 p. m. a severe convulsion occurred and marked hyperextension and opisthotonos developed. These were still present on October 29. The temperature before the injection was about 98 to 99°; for four days after the injection it rose to 102° and once reached 104°.

The conditions which developed in this child following the last injection of serum, after an interval of 16 days since the preceding injection, cannot be explained readily. We prefer to leave the

question open whether the phenomena belong to the anaphalactic state or are of another nature. But so far as the case bears on the general question of the intradural injection of the serum it has theoretical rather than practical significance. The antiserum will, as a rule, discharge its beneficial effects in the first days of its employment and for this no danger is known to exist. Rarely, after a resting period in its use, a relapse of the acute infection may call for another injection. The records of the use of the antiserum in relapses do not show that any ill effects followed the injections. We think that the reinjection of the serum in supposed relapses should be based upon demonstrated reappearance of or increase in the diplococcus, since mere sudden rise in the temperature, in the course of meningitis, may obviously be due to other causes than a reinvasion of *Diplococcus intracellularis.*

MANNER OF PREPARING THE ANTISERUM.

The antimeningitis serum employed in the treatment of the cases of epidemic meningitis described in this paper has been made in the horse. The general method of preparation has been as follows:

The first inoculation consisted of cultures of the diplococcus, heated to 60° C. for 30 minutes, injected under the skin. Many different strains of the diplococcus were combined to prepare this vaccine. The first dose was the equivalent of ¼ surface growth on sheep-serum agar in a test tube. The dose was doubled at each subsequent inoculation, until an amount equal to four test tube growths could be given at 5 to 7 day intervals.

Intravenous inoculation was now substituted for the subcutaneous. Beginning with one oese of living diplococci the dose was progressively increased to 2, 3, 5, etc., oese, then ½, ¾, 1, etc., agar slant cultures, and finally to 1½ bottles (12 oz. Blake) of surface growth. The larger quantities of the culture injected into the vein caused such severe reactions and alarming symptoms that they were discontinued.

Subcutaneous and intravenous injection of an autolysate[14] was now used. The doses, at first 1 cubic centimeter, were later increased to 3 cubic centimeters. The injections were made about one week

[14] *Jour. of Exper. Med.*, 1907, ix, 105.

apart. The intravenous injection of the autolysate was discontinued because of the serious symptoms (increased respiration, weakness, etc.) which resulted from them.

At the present time the subcutaneous tissues are being used exclusively for the inoculations, which are made alternately of living diplococci and autolysate at 7-day intervals. Many different strains of the diplococcus are employed in preparing the living cultures and the autolysate for inoculation. The dose of living diplococcus has been increased to one and one half bottles, and of autolysate to the equivalent of one and one half bottles of the cultures.

The febrile reaction to the subcutaneous inoculations is moderate: The temperature rises to 39° to 39.6°. The animal eats less during the febrile period. The local reaction is much greater. Within a few hours a swelling appears at the site of inoculation and extends widely—from the shoulder to the knees at times. The swelling tends to disappear in a few days or, in those instances in which the larger doses of living diplococcus or autolysate are used, sterile abscesses develop which eventually discharge through the skin.

The antiserum has been titrated by the complement-deviation method devised by Kolle and Wassermann,[15] and tested against the autolysate in guinea-pigs. Neither method appears to be quantitatively accurate. The antiserum used in the treatment of the cases of epidemic meningitis described in this paper came from a horse in process of immunization one year or longer before being used for supplying the serum.

Coincidently with our efforts to produce an antidiplococcus serum for use in human beings suffering from epidemic meningitis, Kolle and Wassermann[16] and Jochmann[17] attempted in Germany to prepare such a serum. Only brief reports of the employment of these sera in the treatment of epidemic meningitis have thus far appeared in print. Wassermann[18] has recently reported the results of the treatment of a series of cases of the disease by subcutaneous injections chiefly of his serum, with results which, on the whole, appear

[15] *Deut. med. Woch.*, 1906, xxxii, 16.
[16] *Ibid.*
[17] *Ibid.*, p. 20.
[18] *Ibid.*, 1907, xxxiii, 1585.

to be favorable to the value of the treatment. Schöne[19] treated a still smaller series of cases with Jochmann's serum, partly by the subcutaneous and partly by the intradural method of injection, with results said to have been beneficial, especially where the injections were made into the spinal canal.

GENERAL DISCUSSION.

In view of the small number of cases of epidemic meningitis upon which this paper is based, it would seem the wisest policy, possibly, to defer all general discussion of the results until such time as a larger series of cases treated with the antiserum having been collected, a searching analysis can be made.

On the other hand it seems desirable to recapitulate, at this time, the salient points brought out by the different reports which have been collected in this paper, it being understood that they do not represent conclusions but merely statements of observed facts or obvious deductions from them.

Thus, for example, the records of cases used in the preparation of this paper show that of 47 cases of epidemic meningitis treated with the antiserum, 34 recovered and 13 died. Expressed in percentages, the recoveries equal 72.3 and the deaths 27.6 per cent. The records also show that of the 13 fatal cases four were either fulminant in type, in which death took place within 24 to 36 hours of the onset, or the patient's condition was so extreme that death occurred in a few hours of the injections of the antiserum. If, therefore, these four cases are subtracted there results a total of 43 cases of meningitis treated with the antiserum of which 34 recovered and 9 died, or 79.9 per cent. recoveries and 20.1 per cent. deaths.

This tabulation takes the cases without respect to their duration at the time the treatment was begun. This is manifestly a severe test, but so long as the whole number of cases is so small no other mode of analysis is likely to be as useful. Should it be desired, however, to know the ratio of recoveries to deaths in cases injected with the antiserum in the first three days of illness, the calculation could be based on 18 cases of infection, exclusive of the ful-

[19] *Die Therapie der Gegenwart,* 1907, xlviii, 52.

minant ones, of which 16 or 88.9 per cent. recovered and 2 or 11.1 per cent. died.

In order that these figures should have any value whatever we are obliged to know with what degree of severity the epidemic prevailed at the time and place at which the antiserum was used. We possess, fortunately, good data concerning this point. Eighteen cases of epidemic meningitis occurred at Castalia within a few weeks. Of these twelve patients died and six recovered. Of those patients who recovered three were injected with the antiserum, and no patient having received the serum died.

The report from Akron covers twenty cases of epidemic meningitis of which nine were not treated with the antiserum: Eight died and one recovered. The remaining eleven cases were treated with the antiserum: three died and eight recovered. The three fatal cases included two of the fulminating variety.

Dr. Robb[20] has given statistics covering 230 cases of epidemic meningitis which arose in Belfast. Of these 162 died making a mortality of 70.43 per cent. As regards the severity of the disease at the time at which the antiserum prepared by us was employed he states in his letter (p. 203): "I believe there has been little if any change in the type here."

The majority of the cases which were treated with the antiserum were in children over five years of age and in adults. Since the mortality is highest among young children a table has been prepared, from Dr. Ladd's report, giving the results of the use of the serum in children under five years of age (p. 185). Of the eight children belonging to this group seven were under three years and one was about five years old. Five of the children recovered and three died. Two of the three fatal cases were injected on the fourth day and one on the twentieth day.

The records of the patients who recovered have been full enough in twenty-five instances to enable us to make out the manner of termination of the disease—whether by lysis or by crisis. We have found that thirteen times the disease terminated by lysis and twelve times by crisis. The accompanying table (Table I) illustrates this point and enables the individual case-histories, upon

[20] *British Medical Journal*, 1907, No. 2443, 1129.

TABLE I.

Dr. Ladd's Cases.

Case No.	Day of Disease. First Injection.	Total c.c. Anti-serum Injected.	Recovered by Lysis.	Recovered by Crisis.	Died.
I.	3	25	+		
II.	12	5		+	
III.	4	30	+		
IV.	5	15			+
V.	2	35		+	
VI.	1	15		+	
VII.	3	20		+	
VIII.	3	45	+		
IX.	2	35			+
X.	1	15		+	
XI.	20	25			+
XII.	4	46			+
XIII.	1	45		+	
XIV.	14	28	+		
XV.	3	53	+		
XVI.	4	41			+
Akron Cases.					
I.	5	82.5	+		
II.	1	10			+ F
III.	12	20	+		
IV.	2	43.5	+		
V.	7	25		+	
VI	2	22.5			+
VII.	1	15		+	
VIII.	1	35			+ F
IX.	2	105	+		
X.	1	25		+	
XI.	2	22.5		+	
Pennsylvania Hospital Cases.					
I.	4	15		+	
II.	3	25	+		
III.	4	45		+	+
IV.	11	25			
V.	10	15	+		
St. Vincent's Hospital Cases.					
I.	?	30			+
II.	4	30	+		
III.	?	60	+		
Edinburgh Cases. Recovered (no details).					
I.	—7	120	+		
II.	—7	120	+		
III.	—7	120	+		
IV.	1	30			+ F

		Belfast Cases.			
I.	2	90	+		
II.	2	90	+		
III.	10	90	+		
IV.	2	30			+ F
V.	35	30	+		
VI.	25	60	+		
VII.	?	?			+
		Dr. Cushings' Case.			
I.	56	45	+		

— = less than. F = Fulminating.

which it is based, to be scrutinized. In a number of cases the abrupt termination of the disease, after acute and violent onset, within forty-eight hours of the injection of the antiserum, was striking and impressive. In some cases the serum was injected as early as twelve hours, and in one case as early as two hours, after the onset of severe symptoms, with prompt arrest of the disease.

Once or twice after abrupt arrest of active symptoms lasting several days, relapses occurred which were as promptly controlled by another injection of serum as was the original infection. It would appear that during the height of an epidemic of meningitis spontaneously abortive cases are of infrequent occurrence.

To discuss, on the basis of so small a series of cases as is here presented, whether the antiserum can be said certainly to influence favorably the temperature, mental condition, and such special symptoms as headache, muscular rigidity, paralyses, etc., seems hardly worth while. Moreover an analysis of the reports having these points in view can be made far better by those who have been in daily contact with the ill from epidemic meningitis and have learned, at first hand, to know its protean aspects and variable course. But, on the other hand, it is patent that the successful cases reported here have, almost without exception, made complete and rapid recoveries. There have been few or no long and tedious periods of convalescence, and in one instance only has a permanent defect—in this instance some imparement of hearing—remained.

Our choice of mode of introducing the antiserum into the body, namely into the spinal canal, should be justified. We were led to this manner of employment by two considerations: First, the

theoretical advantage of bringing the antiserum into direct contact with the focus of infection and inflammation, to support which we possess data based on animal experimentation; and second, the knowledge that elimination of colloids, and of crystalloids even, from the blood stream into the cerebro-spinal fluid is a slow and imperfect process in health and probably in inflamed states of the membranes also. Since there appeared to be no danger from this method of introduction of the serum, provided care was exercised, it was chosen; and the cases recorded in this paper bear testimony to its safety. In a few instances the subcutaneous has been superadded to the intradural injection, but whether any advantage is to be derived from such double injections, greater experience will have to determine. Could the subcutaneous be substituted for the intradural method there would obviously be a gain in convenience and probably in safety of general employment of the serum. We think it improbable that the results would be as good by the subcutaneous as they appear to be by the intradural method.

We possess evidence that the direct effect of the antiserum upon the diplococci present in the exudate in the cerebro-spinal membrane is to cause their rapid degeneration and an arrest of their free multiplication. This must be of some advantage to the patient. We have noted remarkable reduction in number and striking evidences of degeneration and loss of power of growth of the diplococcus, twenty-four hours after an injection of the antiserum. An exudate previously sero-purulent may be converted into a merely turbid exudate by an intradural injection of the serum.

The few cases in which the exudate has been really purulent or fibrino-purulent and present in small quantity, as judged by the few drops which could be secured on lumbar puncture, seemed not to be benefited by the serum injections. Whether such cases are very unpromising will have to be determined by wider experience with the antiserum.

Although we have discussed, briefly, the question of anaphalaxis, the cases in which several injections of serum were made, sometimes with considerable intervals between the injections, tend to show that the danger is not a very real or impending one. It can, we think, be neglected in practice for the present.

It is clear that once we accept the fact of the abortive and critically terminating cases as being caused by the antiserum, the early injection of it is to be sedulously sought. The figures, small as they are, also point to better results from the injections made in the first three days of the illness as compared with those made at a later period. And yet favorable effects have been recorded in cases treated in the fourth, fifth and eighth week of the disease. Basing a tentative deduction on the few facts of our present knowledge, we may suppose that as long as living and multiplying diplococci remain in the membranes and their fluid, the serum may be employed with hope or expectation of useful results. The serum is clearly of no avail in the treatment of symptoms resulting from chronic obstructive lesions of the membranes.

The doses of the serum employed thus far rest on an empirical basis. Whether the larger doses which have been used latterly are more efficient than the smaller ones used at first, can be determined only by a wider experience than we have yet had. In test-tube experiments degree of concentration of serum plays an important part in determining injury and disintegration of the diplococcus, since a high concentration of the serum is more effective than a low one. But the mechanism of test-tube bacteriolysis and of intradural bactericidal effect may be and doubtless are widely different. Our knowledge of the manner of *intra vitam* disposal of the diplococcus after serum injection is very defective; but an important factor is doubtless the intracellular, phagocytic digestion for which we have evidence derived from microscopical examination of the cerebro-spinal exudate. While in active stages of the infection the intracellular diplococci present sharp outlines and appear vigorous, and the extracellular microorganisms are well preserved, after the serum injection the diplococci within cells have lost sharpness of outline, stain indifferently, and strike one as degenerated, and those without cells are much reduced in numbers and staining power. Possibly it is this active and apparently accelerated intracellular digestion which prevents an increase in toxic effects following the serum injections such as might otherwise occur from the more rapidly liberated endotoxin. That the antiserum possesses certain direct antitoxic properties, which also tend to di-

minish the dangers of endotoxin-intoxication, would seem to be indicated by its power to neutralize *intra vitam* the toxic effects of an autolysate of the diplococcus.

In order to avoid unnecessary repetition in preparing this discussion, some of the above propositions have been stated in a manner that might readily convey the impression that we regard it evident and established that the antiserum has proven its usefulness as a therapeutic agent in epidemic meningitis. The facts of our belief, at the present time, are quite otherwise. No one could be less convinced of the final fact of its value than we are. On the other hand, we believe that the data at hand warrant a wider trial of the antiserum, particularly as no other and better means of combating the disease is available. We think, however, that it is unjustifiable to employ the serum indiscriminately and without proper clinical and bacteriological controls. We shall be able, at the Rockefeller Institute, to supply a moderate amount of the antimeningitis serum for use under conditions of control which we shall prescribe.

ADDENDUM.

Since the completion of this paper reports of seventeen additional cases of epidemic meningitis in which the antiserum was employed have been received. The full histories of the cases will be published later, but summaries of them will be given here. Twelve of the cases were treated at the Municipal Hospital, Philadelphia, by Dr. Franklin Royer. A tabulation of them follows:

Case No.	Age of Patient in Years.	Day of First Serum Injection.	Total Amount in c.c. of Serum Injected.	Result.
I.	3	7	180	Died.
II.	4	9	90	Recovered.
III.	18	3	90	Died.
IV.	7	3	140	Recovered.
V.	3	4	220	Died.
VI.	10	2	90	Recovered.
VII.	8	6	30	Recovered.
VIII.	22	?	95	Recovered.
IX.	13	3	150	Recovered.
X.	10	8	90	Died.
XI.	10	4	150	Recovered.
XII.	13	3	120	Recovered.

Two babies, each a year old, were treated with the antiserum at Mt. Sinai Hospital, New York, by Dr. Heiman. One received the first injection of serum on the twenty-third day, 60 cubic centimeters were injected in all; it died. The other was injected on the fifteenth day, received 35 cubic centimeters of the serum and recovered.

Two children were treated with the serum at the Babies Hospital, New York, by Dr. Holt. One is eleven months old, was injected first on the forty-ninth day of illness and will probably die. The other is eighteen months old, was injected first on the twenty-third day of illness and is now convalescent.

An additional case, not included in the first series of cases, was treated at the Akron City Hospital. The child was six years old, was injected first on the sixth day of illness, received in all 160 cubic centimeters of antiserum and recovered.